

AMERICAN JOURNAL OF OPHTHALMOLOGY

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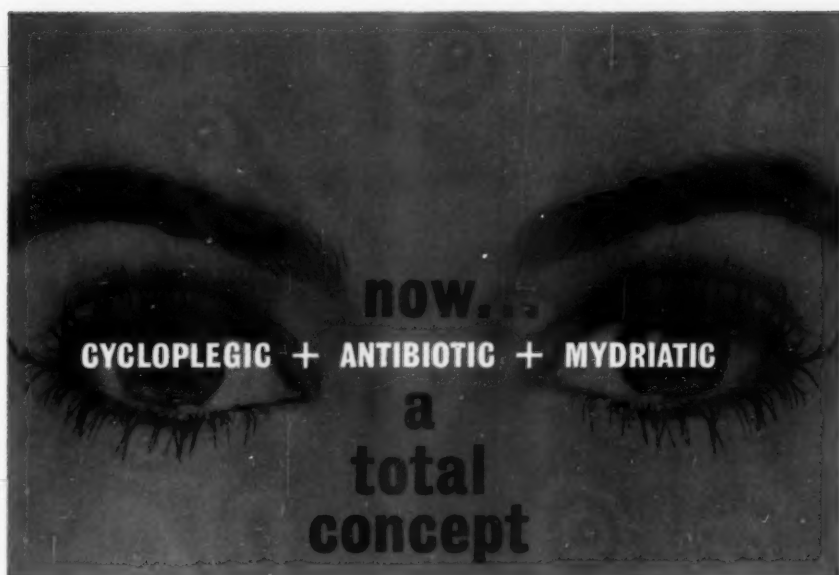
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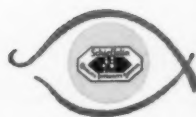
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References: 1. Miles, P. W.: Missouri Med. 56:1243, 1959. 2. Sorsby, A.: Ann. Roy. Coll. Surgeons of England 22:107, 1958. 3. Costner, A. N.: South. M. J. 48:1192, 1955. 4. Rasgorshek, R. H., and McIntire, W. C.: Am. J. Ophth. 40:34, 1955.

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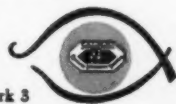
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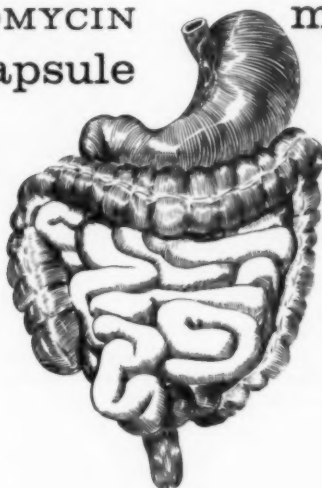
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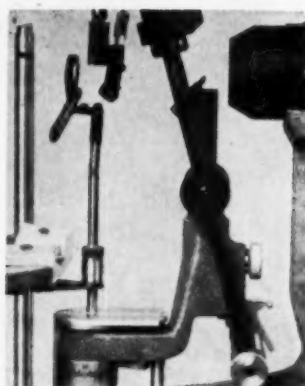
1. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Observations on Demethylchlortetracycline. Presented at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 2. Hirsch, H. A.; Kunin, C. M., and Finland, M.: Demethylchlortetracycline—A New and More Stable Tetracycline Antibiotic That Yields Greater and More Sustained Antibacterial Activity. München, med. Wchschr. To be published. 3. Lichter, E. A., and Sobel, S.: The Distribution of Oral Demethylchlortetracycline in Healthy Volunteers and in Patients Under Treatment for Various Infections. To be published.

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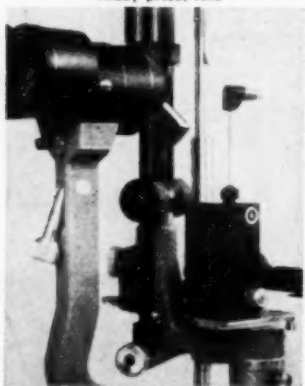
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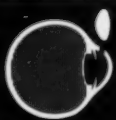
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¹Girard, L. J., Dukes, C. D., and Fleming, T. C. Presented at the International Congress of Ophth., Brussels, Belgium, 1959.

²Kara, Gerald B., "The Use of Alpha-Chymotrypsin in Cataract Extraction," Research Report No. 10, Alcon Laboratories, Inc., 1959.

³Vail, D., et al. Report: Committee on use of alpha-chymotrypsin in ophthalmology. Presented at the Sixty-fourth Annual Session, American Academy of Ophthalmology and Otolaryngology, Chicago, Oct. 11-16, 1959. (To be published)



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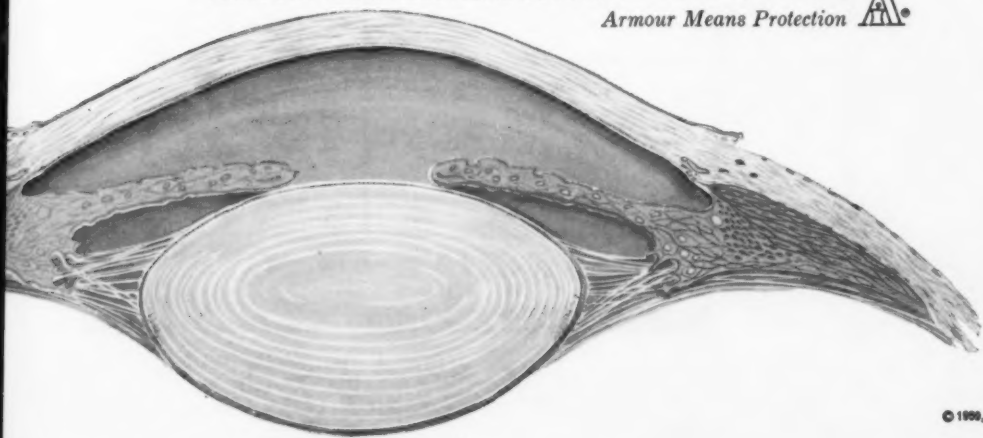
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1. Cogan, J. E. H.: *Proc. Roy. Soc. Med.* 51:927, 1958. 2. Jenkins, B. H.: *J.M.A. Georgia* 45:431, 1956. 3. Raiford, M. B.: *J.M.A. Georgia* 48:163, 1959. 4. Rizzuti, A. B.: *A.M.A. Arch. Ophth.* 61:135, 1959.

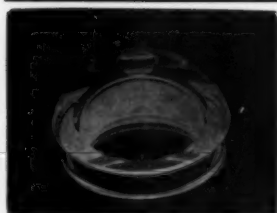
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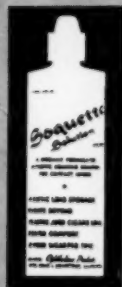
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¹CLIFTON, C. E. AND HALL, W. C. "RE-STERILIZING ACTIVITY OF CERTAIN CONTACT LENS SOLUTIONS." CONTACTO, THE CONTACT LENS JOURNAL, 3:10, 301-3, 1959.

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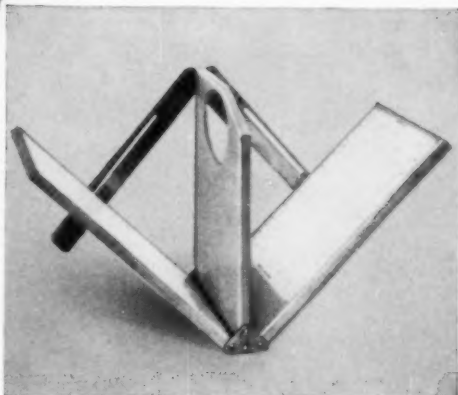
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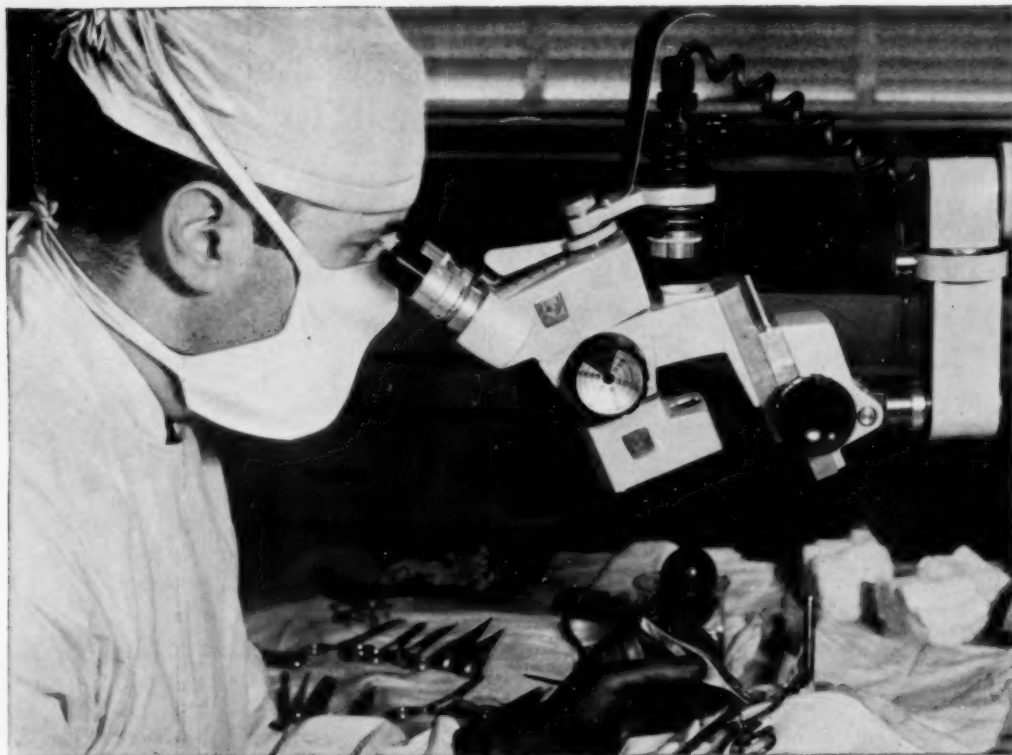
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Antibiotic-Steroid Ointment for Ocular Infections

Wider antibacterial spectrum. Increased therapeutic efficacy. Clears infection...relieves inflammation. Combats both gram-positive and gram-negative invaders. Minimizes emergence of resistant strains. Lessens danger of scarring. Needs no refrigeration. Virtually free from irritative or allergic properties.

INDICATIONS: Provides wide-spectrum antibacterial, anti-inflammatory, and antiallergic action for topical treatment of patients with ocular inflammation complicated by infection.

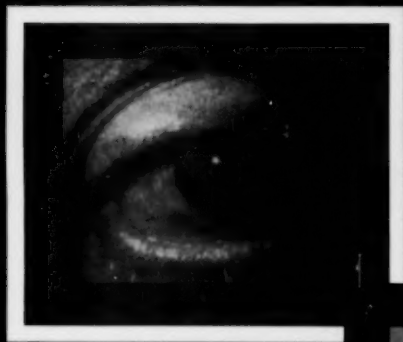
ADMINISTRATION: Apply two to four times daily as required.

PACKAGING: OPTHOCORT Ophthalmic Ointment contains 1% Chloromycetin® (chloramphenicol, Parke-Davis); 0.5% hydrocortisone acetate, and 5,000 units polymyxin B sulfate per gm., supplied in 1/2-oz. tubes.

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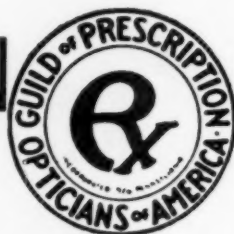
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retinal hemorrhages absorbed with use of

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NO IODISM

As shown by retinal photography, rapid absorption of retinal hemorrhages follows use of IODO-NIACIN. These results have been established in a series of 22 cases, 12 of retinal and 10 of vitreous hemorrhages.¹

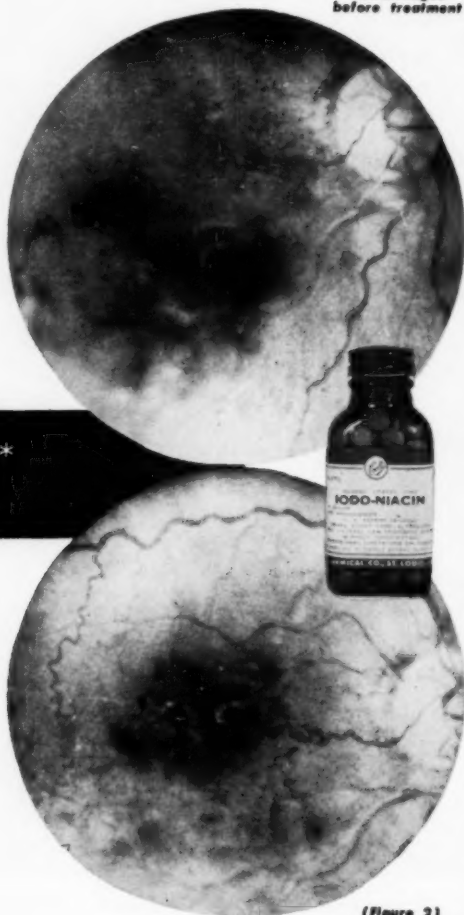
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IODO-NIACIN may be administered in full dosage for a year or longer without any iodism or ill effect.²

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Cole CHEMICAL COMPANY
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(Figure 1)
Retinal
hemorrhages
before treatment



(Figure 2)
After 18 days'
treatment with
Iodo-Niacin

1. *Am. J. Ophth.* 42:771, 1956.
2. *Am. J. Digest Dis.* 22:5, 1955.
3. *Med. Times* 84:741, 1956.

* U.S. Patent Pending

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Ample diuresis for the usual edema-
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Scored tablets of 250 mg. Ampuls of 500 mg. for parenteral use.



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During analysis, as your patient's corrective needs begin to take shape on paper, you are entitled to a sense of accomplishment.

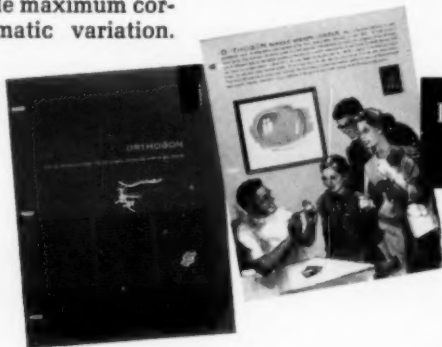
Now your decision—not merely to recover lost acuity, but to provide the greatest possible visual achievement—can reinforce your sense of accomplishment.

When you write "Orthogon" on the prescription, you can be sure that no aspect of lens quality will be lacking. Orthogon lenses—and only Orthogon lenses—provide maximum correction for marginal astigmatic variation.

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All the features and applications of Orthogon lenses are contained in "Bausch & Lomb Ophthalmic Lenses"—a reference catalog recently mailed to you—Orthogon types, power range, availability, and other valuable material on lens theory, manufacture and fitting.

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- Double-wound transformer for safety.
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1633G:

1632G:



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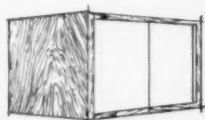
ADAPTA-ROD cabinets are the practical answer to space problems in your office. They're easy to have, too, with the American Optical Pay-As-You-Grow Plan. Take up to five years to pay for the office you want now. Mail coupon today for details.

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THREE-DAY SEMINARS / LENS ADJUSTMENT SEMINARS



TIME: All seminars will be held from 10 a.m. to 5 p.m. daily.

THREE-DAY SEMINAR: A comprehensive course of study designed to provide information and practical knowledge that can assist you in successfully fitting contact lenses. The latest techniques and developments will be presented such as fitting SPHERCON®, Bi-Curve and Tri-Curve lenses; the use of the new TORCON* lens in fitting unusual astigmatism cases; the techniques of fitting BICON®, de Carle, and C. B. bifocal contact lenses; TELECON*, a recently introduced subnormal vision aid; Photo-Electronic-Keratometry (PEK*), its theory and use; CONTA-SONICS*, an invaluable aid to the practitioner.

To gain practical experience, each practitioner who registers for this course will receive a personal pair of contact lenses, which will be fitted in class. Your K-readings and Rx must be included with your registration so that your lenses can be processed prior to course date.

ONE-DAY LENS ADJUSTMENT SEMINAR: Provides the basic theory and practice required to perform all contact lens adjustments. This course to include: The CON-LISH* process of uniform edge finishing; methods of applying a CN bevel; grinding, polishing, and blending of intermediate and peripheral curves. The fundamentals of proper lens inspection will be fully demonstrated. Skill in lens inspection will enable you to objectively verify each lens adjustment you make.

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February 23-24-25
March 1-2-3
March 8-9-10
March 15-16-17
March 22-23-24
April 5-6-7
April 12-13-14
April 19-20-21
April 26-27-28
May 3-4-5
May 10-11-12
May 24-25-26
June 7-8-9
June 14-15-16
June 21-22-23

Lens Adjustment Seminars

February 26
March 4
March 11
March 18
March 25
April 8
April 15
April 22
April 29
May 6
May 13
May 27
June 10
June 17
June 24

City and State

Memphis, Tennessee
Detroit, Michigan
Washington, D. C.
Salt Lake City, Utah
New York, New York
Los Angeles, California
Phoenix, Arizona
Miami, Florida
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Dallas, Texas
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†This Seminar will be held at the Wesley/Jessen Contact Lens Company, Vision Building, 635 Madison Ave., New York 22, N.Y.

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Please mail to THE PLASTIC CONTACT LENS COMPANY, 5 South Wabash Avenue, Chicago 3, Illinois. A \$25.00 DEPOSIT IS REQUIRED WITH ALL REGISTRATIONS. CHECK THE SEMINAR YOU DESIRE TO ATTEND:

Note: If registering for the Three-Day Course, be sure to include your K-readings and Rx so we may process your lenses prior to seminar date.

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- ☐ Enclosed is my registration check for \$65.00 for the Three-Day Contact Lens Seminar.
- ☐ Enclosed is my registration check for \$27.50 for the One-Day Lens Adjustment Seminar.

(Date of Seminar) _____ City _____

Name _____

Your Mailing Address _____

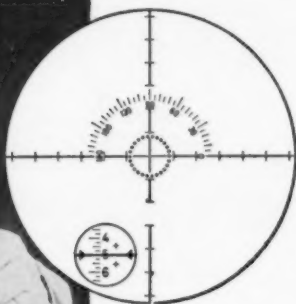
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RECORD K-READINGS AND YOUR RX HERE:

K-Readings: O. D. _____ O. S. _____

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ZEISS PUNKTAL LENSES . . . classic white lenses that give a point focal image and broad field of vision throughout the lenses, are available in a wide range of powers.

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For your protection every lens bears this symbol of perfection.



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For the doctor, the patient, dispenser and/or laboratory, Catarex Service offers many positive benefits. Next time you are involved in a cataract case, ask about this splendid service!

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STRABISMOMETER

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Quick-Easy Diagnosis

THE ALLIED RECTANGULAR CO-ORDINATE TANGENT SCREEN

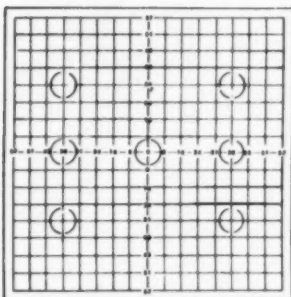
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Complete kit consists of: 2 hand projectors - transformer - red and green spectacles - instruction manual

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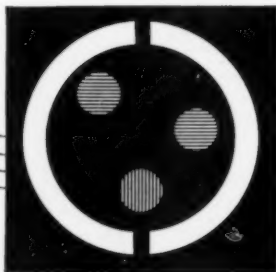
54 in. Screen and Roller, Pad of Recording Charts \$20.00 additional.
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Rapid efficient
post-surgical test
of peripheral fusion
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AMERICAN JOURNAL OF OPHTHALMOLOGY

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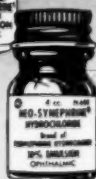
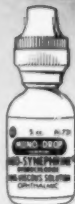


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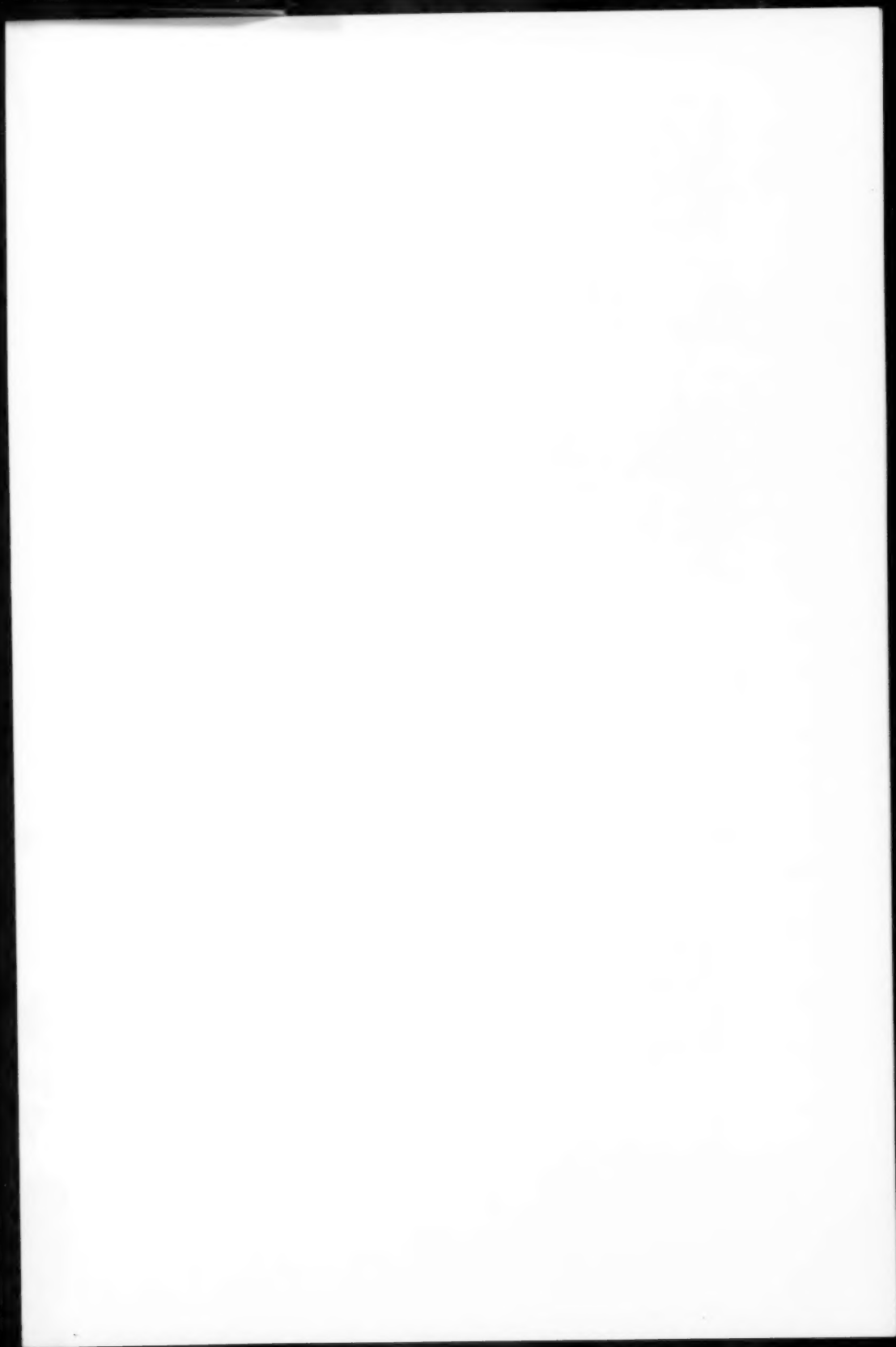
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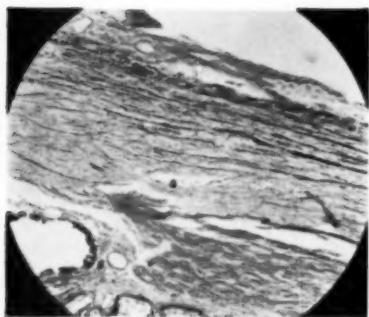


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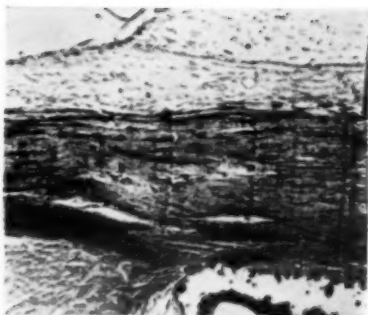


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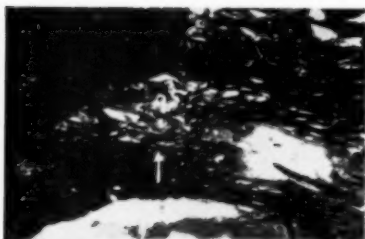


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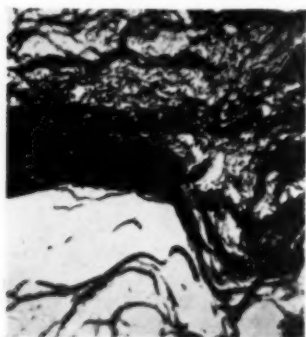


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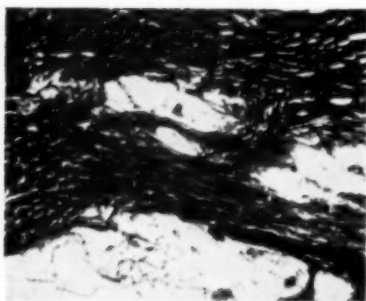


Fig. 5

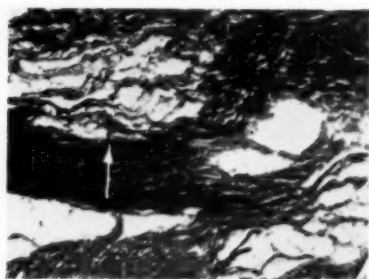


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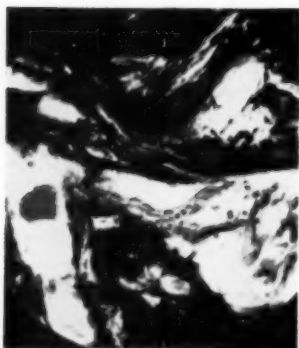


Fig. 7

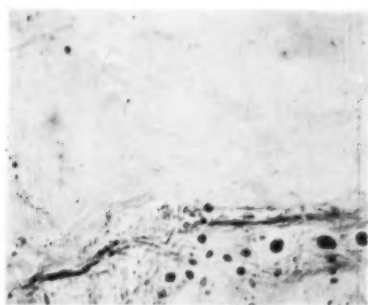


Fig. 8

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HISTOLOGIC OBSERVATIONS OF THE STRUCTURE OF THE SCLERA IN GLAUCOMATOUS HUMAN EYES*

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It seems to be commonly held that the main outflow of the aqueous is through the trabecular tissue to Schlemm's canal and from there along the aqueous veins, scleral plexuses and collector channels to the episcleral veins. Fluorometric (Goldmann¹) and tonographic (Grant, 1950,² Moses and Bruno, 1950³) examinations have proved that there is decreased facility of the aqueous outflow in simple glaucoma, obviously on account of increased resistance. Resistance to the outflow is not constant in a given eye.⁴ The location of the resistance has been placed at different points of the trabecular meshwork,⁵⁻⁹ outside Schlemm's canal,¹⁰ in the collector channels,¹¹ or in the intrascleral veins.¹²

Teng, Paton and Katzin¹³ found in simple glaucoma degenerative changes that they regarded as primary in the fibers of the tra-

becular meshwork and proliferation in the endothelial cells there and also in Schlemm's canal and the collector channels. According to the view held by Ashton and his co-workers,¹⁴ the changes mentioned could, however, be artefacts. In a later work, however, Teng, et al.¹⁵ confirmed their findings.

In considering the possible significance of the sclera for drainage it must be remembered that its embryonic development and structure show special features not only in the areas of the scleral trabecular meshwork but also generally in the anterior part of the sclera.¹⁶⁻¹⁸ The orientation of the fibers, their structure as well as the ground substance in the sclera proper aroused our interest in the extent to which these factors might affect the outflow in a glaucomatous eye and be histologically observed.

MATERIAL AND METHODS

The material comprised 15 eyes with absolute primary glaucoma enucleated after 1954: 10 simple glaucoma and five closed-angle glaucoma eyes, and 12 eyes with normal

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Figs. 1-8 (Vannas and Teir). Histologic observations of the structure of the sclera in glaucomatous human eyes.

Fig. 1. A woman, aged 69 years, with absolute simple glaucoma. Tubularlike structure is visible only as shadows. (Meridional section, lead acetate—Mallory, X80.)

Fig. 2. Meridional section of a closed-angle glaucoma eye in a woman, aged 71 years. The degenerative changes of the anterior sclera are obvious. The reddish color and some unusual fibers are apparent in the inner part of the sclera. Perpendicular tubularlike structures are partly visible. (Lead acetate—Mallory, X80.)

Fig. 3. Eye of a 70-year-old woman (normal tension) enucleated for malignant melanoma of the choroid. Lacunar spaces in the vicinity of a collector channel (†) behind Schlemm's canal. The cornea (top, right). (Tangential section, lead acetate—Mallory, X80.)

Fig. 4. Extensive atrophy of scleral fibers at the so-called scleral drainage area in absolute closed-angle glaucoma eye. (Tangential section [somewhat oblique], Helly-Mallory, X32.)

Fig. 5. Atrophic changes around the collector channel in a simple glaucoma eye at the "fere absolute" stage. (Tangential [slightly oblique] section, Mallory, X80.)

Fig. 6. A woman, aged 68 years, with absolute simple glaucoma. Severe degenerative changes and empty-looking holes both in the trabecular meshwork and behind Schlemm's canal (†). (Tangential [slightly oblique] section, lead acetate—Mallory, X80.)

Fig. 7. The tangential section view near the limbus in an eye with simple glaucoma. Empty-looking spaces around the anastomosing veins. (Lead acetate—Mallory, X500.)

Fig. 8. Blue-staining granules around a small vein and in superficial scleral tissue demonstrate the presence of mucopolysaccharide. (Tangential section of an eye with simple glaucoma, amino acidine—"Astra Blau," X160.)

pressure enucleated because of trauma or tumor.

The eyes were divided and fixed immediately after enucleation. We employed mainly four-percent basic lead-acetate fixation for 48 hours at room temperature. A great part of the specimens were, moreover, fixed in Helly's solution or 10-percent neutral formol or 0.4-percent amino acridine (Williams and Jackson¹⁹) solution for different investigations.

The eyes were divided into several fragments by radial incisions from the center of the cornea and these were embedded in paraffin. The whole anteroposterior fragment was used for meridional sections and the anterior, nearly triangular piece mainly for tangential sections.

To be able to observe outflow pathways through the sclera we prepared tangential serial sections from normal and glaucomatous eyes. The task was very delicate, difficult, and time-consuming because of the easy distortion and separation of the tissue planes. The sections were 4.0 μ thick and cut outward from the inner surface. Since this triangular piece is curved, we tried to flatten it before embedding in paraffin; sometimes the ciliary body is, for the some purpose, prepared off. In spite of this, often only one part of the specimen is fully parallel with the surface and the other part is somewhat obliquely cut. Up to 300 sections were made from a single eye.

The majority of the sections were treated with mercuric chloride and then stained with Mallory's trichrome stain.¹⁸ Sulfated or non-sulfated mucopolysaccharides were demonstrated with methylene blue; periodic acid Schiff (PAS) and "Astra-Blau" (Bayer)²⁰ staining were also used, for the demonstration of neutral and acid mucopolysaccharides.

FINDINGS

A. SCLERAL STRUCTURE IN MERIDIONAL SECTIONS

In a meridional lead acetate-mercuric chloride-Mallory section of the control eye the

collagenous fibers running anteroposteriorly stained blue. Between them, in the region of the crosscut collagenous fibers, there were more or less reddish-brown or grayish areas in which were seen various unusual tortuous fibers and tubular structures.

In transverse sections the structure of the sclera seemed somewhat similar to that in meridional sections since the circular fibers stained blue and the areas between them showed red-staining with the structures mentioned.

There was considerable variation in control eyes in red-staining and the presence of the tubular structures due to aging and methodical difficulties. The view of the meridional sections of the control eyes thus correspond with that obtained earlier by the same technique.^{17, 18}

Glaucomatous eyes

The red-staining in the anterior part of the sclera was generally faint, but more intensive in the inner side; there was, however, considerable variation in the red-staining, as in aged eyes with normal pressure.

In a *simple glaucoma* (fig. 1) eye, the fibers, running in pairs perpendicularly between the meridional collagenous bundles, so-called tubular structures, were fairly delicate and sometimes appeared only as shadows in the anterior part of the sclera and especially in the vicinity of Schlemm's canal. Unusual tortuous fibers, staining dark-brown, were scarcely visible there and evidently fewer in number than in control eye.

In a *closed-angle glaucoma* eye (fig. 2) the unusual fibers were visible and sometimes abundant, especially in the inner part of the sclera before and behind Schlemm's canal. In the outer part in the region of the exit veins, unusual fibers and tubular structures were few and collagenous bundles showed atrophic changes in this vascularized area. At the level of the ora serrata and behind it almost no variations from control eyes were found.

B. SCLERAL STRUCTURE IN TANGENTIAL SERIAL SECTIONS

The structural specialization of the anterior part of the sclera emerged clearly in tangential sections fixed in lead-acetate solution. The posterior part of a control eye was more compact and the interlacing blue collagenous fibers, which run featherlike in different directions, formed lamellae. Next to the connective tissue cells there were, however, empty-looking small pores.

In the anterior part (fig. 3) of the sclera the view showed considerable variation in the shape, direction, and constitution of the scleral fibers. The structure was more compact in the interior of the sclera, especially backward from the scleral spur. Behind Schlemm's canal and around the collector channels a special arrangement of the lacunar spaces was seen.

We shall confine our examination here to the surroundings of the outlet pathways of the anterior sclera and this porous tissue, so-called *scleral drainage area*, in glaucomatous eyes.

A *closed-angle glaucoma* eye (fig. 4) shows a far-advanced absolute phase indicated by extensive atrophic changes and loss of collagenous fibers and destruction of ground substance in the scleral drainage area.

In a *simple glaucoma* eye at the "fere absolute" phase (fig. 5) we see in the oblique section that the vein leading backward from Schlemm's canal is somewhat dilated and that there are atrophic changes around it and even farther away. Atrophic changes in collagen fibers and holes and spaces are very striking both in the trabecular tissue and around the collector channel (fig. 6), which illustrates the condition in an eye with absolute glaucoma of long standing.

In tangential sections from outside Schlemm's canal can be seen in the region of the scleral drainage area both the prominent porous structure of the sclera and the numerous veins which are surrounded by empty-looking lacunar spaces.

Superficially and farther back as well, the scleral structure was mainly fairly tight. But some empty-looking pores were visible there, too, close to the aqueous veins (fig. 7).

Empty-looking pores and spaces were thus obvious, especially in the region of the outlet pathways. This was a rather surprising finding in glaucomatous eyes, in view of the fact that these eyes usually have an increased resistance to outflow; it could contradict the significance of the sclera as a barrier to outflow.

C. MUCOPOLYSACCHARIDES IN THE SCLERA

A possible resistance in the anterior sclera could depend on the amount and behavior of the gel-like ground substance, in the spaces, already described, around the outlet pathways. This ought to be reflected from the mucopolysaccharide content of the connective tissue. To clarify these questions we used various methods of detecting the presence of mucopolysaccharides of different types, in the anterior sclera especially.

It might be thought, then, that the labile red-staining in lead acetate-mercuric chloride-Mallory sections could be attributable to a component of the ground substance of the connective tissue or to a component of the cement substance of the collagenous fibers. It was, however, resistant to bovine testicular hyaluronidase. In mucopolysaccharide stainings it was negative to PAS and methylene blue.

With the amino acridine¹⁹ and Pioch's²⁰ "Astra-Blau" technique of demonstrating acid mucopolysaccharides we observed in the tangential sections blue-stained granules of various sizes in the sclera. They were scattered in the tissue diffusely as fine grains or grouped in bigger lumps. In these cases the structure of the sclera sometimes seemed edematous. At some places a small blue area was seen around the tissue fibroblasts but no empty-looking pores.

In control eyes the blue staining could come into view outside Schlemm's canal and in the vicinity of the collector channels. The

inner part of the sclera backward from the scleral spur often presented blue staining. It was also found at some places in the outer part of the sclera, for example, around the veins and near the limbus. The spaces seen in lead-acetate fixed series were scarcely visible. With the technique used we never saw any blue staining in the trabecular tissue, despite some blue heparinocytes there.

In a *simple glaucoma* eye at the absolute phase the blue staining in scleral tissue near Schlemm's canal was less evident on the whole than in control eyes. But farther behind in the inner part of the sclera the blue staining appeared to be nearly the same as in the control eyes. On the other hand, in the outer part of the sclera it appeared at some places, for example, near the limbus and also further behind around the exit veins, rather profusely (fig. 8). At these places it seemed to exist more abundantly than in the control eyes. Considerable variations are possible.

DISCUSSION

The material consists of eyes enucleated for absolute glaucoma. The difficulty of obtaining fresh eyes in the initial or intermediate phase of glaucoma has always been a problem in histochemical examinations of glaucoma. At the absolute phase the possibility of differentiating between primary and secondary changes becomes more difficult.

In closed-angle glaucoma eyes we noticed extensive degenerative changes and loss of collagen and empty-looking spaces at the scleral drainage area. These changes evidently are secondary and might follow an overburden and congestion in the anterior ciliary vein and its branches when the outflow via Schlemm's canal is obstructed. According to Vail,²¹ in many cases the neurovascular crisis of uveal erection is the result and not the cause of the acute closure of the angle.

In eyes with simple glaucoma at the almost absolute or absolute phase we also noticed degenerative changes of the collagen at the scleral drainage area, but in less degree.

These changes were most clearly visible in the vicinity of Schlemm's canal and the collector channels. Teng, et al.¹⁸ also described degeneration and gradual loss of staining property of collagen outside Schlemm's canal and the collector channels in four eyes with simple glaucoma at the intermediate phase.

We found in the meridional Mallory sections made from the sclera of glaucomatous eyes and fixed in lead acetate, reddish-gray areas between the blue fibers running meridionally. These areas showed tortuous, unusual fibers, often in pairs, and tubular structures with a course perpendicular to the outer and inner surface of the sclera. The shape of these structures displayed considerable variation even in aged eyes with normal pressure.¹⁹ The same applied, perhaps to an even greater extent, to glaucomatous eyes.

In the areas between the meridional fibers we are concerned with a mass constituted, for instance, of obliquely or cross-cut collagenous fibers and the ground substance. The collagenous fibers and the ground substance may be arranged in major morphologic units, and the collagen molecules grouped in different ways forming macromolecules of differing direction and shape.^{22,23} Such changes may be due to the altered chemical conditions of the fibers and the ground substance. The change of the ground substance depends greatly on the condition of the mucopolysaccharides.²³

To what extent the perpendicular structures mentioned could further fluid transportation, we cannot decide. The importance of the suprachoroid space for the drainage of a glaucomatous eye is indicated by the experience of earlier authors (M. Vannas,²⁴ Barkan,²⁵ Csillag²⁶) that the optimal result after some glaucoma operations (cyclodialysis, and so forth) usually follows only if a communication is achieved from the anterior chamber to the suprachoroidal space. The location of tubular structures perpendicular to the inner surface of the sclera could

offer a partial explanation of this.

Whether there is resistance also in the spaces and pores described in tangential lead acetate-mercuric chloride-Mallory sections outside the trabecular meshwork might depend on the extent to which there is active gel-like ground substance in them and in the collagenous bundles surrounding them. Such a mechanism would be in agreement with investigations by Wassermann²³ and others concerning the interrelationship of collagenous fibers and ground substance in connective tissue generally.

The presence of a hyaluronidase-sensitive barrier to the outflow was stated by the perfusion experiments of Bárány²⁷ who found that, regardless of the enzyme source, an approximately 50-percent decrease in outflow resistance could be achieved in some species. This is confirmed by Berggren and Vrabec²⁸ and by the microradiographic studies of François, Neetens and Collette.²⁹ According to the investigations by Vrabec,^{7,28} Brini,⁸ and Zimmermann,⁹ the trabecular meshwork has a mucopolysaccharide-containing ground substance, sensitive to hyaluronidase, which functions as a resistance to the outflow.

Cattle sclera swelled more in the anterior than in the posterior part, as stated by Nakamura³⁰ who assumed this to depend on a higher concentration of ground substance in the anterior part.

Wortman and Strominger³¹ indicated the presence of mucopolysaccharides electrophoretically in cattle sclera; they tested an acid mucopolysaccharide with the electrophoretic mobility of chondroitin sulfate, and, like chondroitin sulfates A or C, it was degraded by testicular hyaluronidase. Smelser and Ozanics³² demonstrated histologically the presence of mucopolysaccharides in the fetal rabbit sclera. These mucopolysaccharides disappeared at the time of birth.

We observed acid mucopolysaccharides in the anterior sclera, specifically around the exit veins. This blue-staining material,

sometimes found around the scleral fibroblasts, corresponded somewhat to the small pores in the lead acetate-mercuric chloride-Mallory slides. The location of the blue staining in the vicinity of the outlet pathways makes it theoretically possible that it could function as an outflow barrier.

The presence of acid mucopolysaccharide around the exit veins could result in closure of the veins and obstruction to aqueous outflow. However, such a mechanism was suggested earlier by Theobald and Kirk,¹² as secondary to hypertrophy and sclerosis of the sclera.

Acid mucopolysaccharide in the intertrabecular spaces demonstrated with the alcian-blue or colloidal iron (Rhinehart-Abul-Haj) techniques^{8,9} was not observed with the method used by us. The method used gave a blue presentation only with some heparinocytes in the trabecular tissue.

Acid mucopolysaccharide was observed in the anterior sclera both in glaucomatous and control eyes. Its significance as a resistance to outflow can depend on the location, amount and state of swelling of mucopolysaccharides and needs further investigation.

SUMMARY

The anterior part of the sclera in 15 eyes with absolute primary glaucoma was examined for the occurrence of unusual connective tissue structures and ground substance. Degenerative changes and loss of collagen were noticed there. With the aid of delicate tangential serial sections, lacunar spaces were found, especially behind Schlemm's canal. They seemed to be dilated in glaucomatous eyes. Acid mucopolysaccharide was demonstrated in the vicinity of exit veins. It was assumed to have the role of a possible extravascular control of intraocular pressure. The findings in eyes with simple and closed-angle glaucoma were compared with those in normal eyes.

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THE CORRECTION OF UNIOCCULAR APHAKIA BY MEANS OF ALL-ACRYLIC ANTERIOR CHAMBER IMPLANTS*

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I was delighted to receive your secretary's kind invitation to address you today for several reasons. Firstly, on a personal note, during World War II, I was in the British Navy, and for about 18 months we were on the North Atlantic run, and did, on one occasion, visit Mobile and New Orleans, but only briefly. I was fascinated by my fleeting glimpses of your country and have always hoped for an excuse to revisit the United States.

Secondly, as you know, in England today we have the National Health Service. Brought into being no doubt with the best of intentions, it has nevertheless created an administrative machine so top heavy that it is in the process of slowly but surely crushing the life out of our medical profession. By this I mean that by the time a maximum part-time consultant, like myself, has dealt with his administrative and clinical chores, he has neither the time nor the energy left for any constructive thinking or research projects. Those of us who are concerned about the future of our profession are coming to realize more and more that our only way of surviving and keeping up with contemporary thought is by travel, either to European clinics or more especially to American clinics, and I know that I stand to learn more from you during this trip than you will learn from me.

Thirdly, and not withstanding what I have just said, I have managed to do an extensive piece of clinical research, numbering well over 100 cases during the past three years. The early results in this series have exceeded

my most optimistic expectations, and I am naturally hopeful that they will continue to prosper. It is my privilege to tell you about this work, and I shall look forward when I have finished to hearing your criticisms, suggestions, and observations.

This problem is best considered under the following headings:

I. Why use an intraocular implant?

II. What sort of implant should be used?

III. How should it be used?

IV. What complications may be encountered?

V. What percentage of success can be expected?

VI. What impact, if any, does this work have upon the more general problems encountered in ophthalmology?

I. WHY USE AN INTRAOCULAR IMPLANT?

In civilized countries, such as yours and mine, where the arts of the dispensing optician and the skill of the contact-lens practitioner have been raised to high levels, patients suffering from binocular ametropia, either high myopes or high hypermetropes, should be corrected to their satisfaction either by spectacles or by contact lenses. This disposes of the problem of binocular aphakia.

There are, however, numerous persons who for one reason or another have at some time during their life developed cataract, or become aphakic in one eye only, the other eye being normal. Having dealt with the cataract, their unioocular aphakia presents a challenge to the ophthalmologist.

The unaided vision of a previously emmetropic eye rendered aphakic by trauma, either accidental or surgical, or a combination of both, is less than 20/400. Therefore, the patient will use the uninjured eye so that the aphakic eye, although potentially useful, contributes very little to the visual require-

* From the Southend Group of Hospitals, Essex, and the Hospital for Tropical Diseases (University College Hospital), London. Presented at the annual congress of the Louisiana-Mississippi Ophthalmological and Otolaryngological Society, Edge-water Gulf, Mississippi, May 15, 1959.

ments of the patient from that time on.

The visual acuity can be restored to normal by the use of a spherical or spherocylindrical combination at spectacle distance; with binocular aphakics this gives satisfactory results in spite of certain disadvantages, namely the patient has to turn the head instead of the eyes in order to look to the side; spherical and chromatic aberration are difficult to avoid with powerful convex lenses approximately 10 to 15 mm. in front of the cornea, though these aberrations can be minimized by skillful dispensing; also there is often difficulty in judging distances. The glasses tend to be heavy and to slip up and down the patient's nose, altering the focal length each time they do so, introducing another reason for dissatisfaction.

Spectacle lenses, however, fail to correct cases of unocular aphakia, principally because of aniseikonia. This will amount to between 28 and 33 percent, assuming that both eyes were previously emmetropic, the slight variation depending on the back vertex distance. To a patient previously accustomed to binocular vision, such a degree of aniseikonia constitutes an insurmountable barrier to fusion and leads to intolerable diplopia. So that a spectacle correction cannot be worn, unless the good eye is occluded.

Contact lenses reduce this aniseikonia to about 10 percent and thus provide a partial answer to the problem of the unocular aphakic patient. This degree of aniseikonia can be tolerated by a few patients. Some authorities claim up to 90 percent of success with contact lenses but their cases have usually been carefully selected. Also, if their cases are reviewed five years later, it will be seen that a high proportion of the patients have discontinued wearing their lenses for various reasons. Certain occupations, such as working in steamy or dusty atmospheres, or in the tropics, are not compatible with wearing them. In addition, it is not possible to fit them to children under the age of seven or eight years, so an important group of patients is at once excluded from the benefits

of contact lenses. As will be seen later, such eyes rapidly become densely amblyopic and fail to respond to restoration of a normal optical system when older and more co-operative.

Contact lenses cannot be fitted to eyes where the cornea has been badly traumatized, so another group of cases has to be excluded from their benefits. Few elderly patients with unocular aphakia are interested in being fitted with them provided they can see well with their good eye. So that the antecedent cataract surgery has been, for this class of patient, something of a waste of time and effort and surgical resources. It is thus seen that contact lenses represent only a partial answer to the problem of unocular aphakia, and there are thus compelling reasons why the possibilities of the correction of aphakia by means of an intraocular correcting lens should be explored.

II. WHAT SORT OF IMPLANT SHOULD BE USED?

It is obviously a serious matter to insert an implant into a human eye. In addition to the usual risks associated with intraocular procedures, the surgeon must be satisfied that the implant will not irritate the eye over a long period of time, nor undergo molecular change which would destroy its physical properties, nor fracture due to the minor trauma to which every eye is subjected in the course of a long life, and will not split up into its component parts due to the chemical action of the intraocular fluids. He must also be certain that it will not set up sympathetic ophthalmia.

First let us consider the question of posterior chamber lenses (the Ridley lens and its modifications). The Ridley lens cannot be introduced in the presence of any adhesions between the iris and posterior lens capsule. Nor can it be inserted if the posterior capsule is missing or defective. Therefore, it must be inserted at the same time as an extracapsular cataract extraction is carried out.

In this series of 111 cases, none of these

requirements were fulfilled; either preliminary surgery had already been carried out on the iris or the lens, or the case was not suitable for the extracapsular operation. Therefore, the Ridley lens could not have been used on any of these cases, and therefore I don't have to discuss the posterior chamber lens at this time.

I would like to say, however, that I had the privilege of working closely with Mr. Ridley during my early years as a trainee ophthalmic surgeon, and I shall always be grateful to him for the encouragement and tuition which he gave me, and I should also like to say that I am very proud that the initial demonstration that the visual defect in aphakia can be corrected by an intraocular lens was made by this compatriot of mine.

The suitability of anterior chamber lenses must therefore be considered. The credit for the first successful use of an anterior chamber lens belongs to Benedetto Strampelli of Rome. He gave a description of this method and the dimensions of his anterior chamber implant in a paper read at Pavia during the session in December, 1953, of the Società lombarda di Oftalmologia (*Ann. Ottal. & Clin. Ocul.*) 53: (No. 2) 1954:

These special lenses take the form of a meniscus of about 12 mm. radius (mean curve of the sclerotic) and a roughly rectangular shape, the shorter side being 4.5-5.0 mm. and the longer about 11-12 mm. In the central part of the lens is the optical part proper, while the remainder is designed to ensure a fit. Of the two short sides of the lens,

one ends in a blunted point, and the other has a central incision so as to end in a dove-tail.

Strampelli did not give the thickness of the haptic portion of the implant, but this appears to have been about 0.91-0.95 mm. He described using this implant in cases of unioocular and binocular aphakia, and also to correct the refractive error of high myopes and hypermetropes who still retained their crystalline lenses. The two principle complications which arose which he mentioned were:

1. Damage to the posterior surface of the cornea, resulting in endothelial corneal dystrophy.
2. Iritis and cyclitis, causing secondary glaucoma.

Even so, he achieved many successes and his work was taken up by Joaquin Barraquer in Barcelona. Both these surgeons used one-piece all-acrylic implants for their initial work. They both emphasized that the implant must be a rigid fit and not move about the anterior chamber, which would set up secondary glaucoma. More recently, other surgeons have been experimenting with implants consisting of a central optical portion, supported by nylon loops (Dannheim and Lieb and Guerry), or tantalum loops (Wynne Parry), the use of which is open to the following criticisms:

1. These implants are designed to last for a patient's lifetime and one must be absolutely sure that the materials of which they are composed are not going to irritate the eye. While it is established that acrylic (fully polymerized methyl methacrylate) will not irritate the eye, the position is less certain with regard to nylon and rather doubtful with regard to tantalum. Paul and Fry have recently investigated the reaction of the choroid and retina of rabbits to various suture materials. They used 6-0 plain gut, chromic gut, silk and nylon. At all postoperative stages silk caused no undesirable inflammatory reaction. Chromic gut was not tolerated quite as much as silk, and nylon produced quite a severe reaction. Nylon produced a

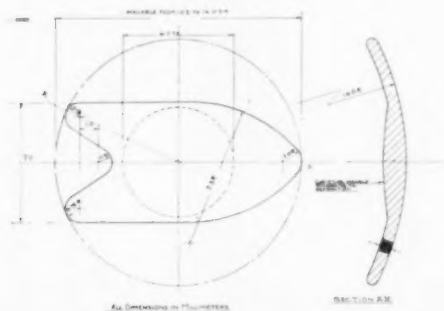


Fig. 1 (Choyce). Choyce implant for the anterior chamber. (Rayner, London.)

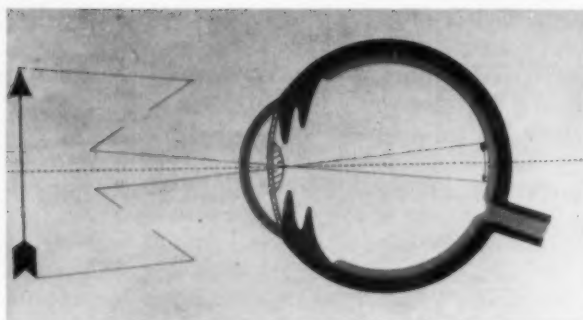


Fig. 2 (Choyce). To show path of rays of light in aphakia corrected by anterior chamber implant.

foreign body granulomatous reaction accompanied by cystic degeneration of the retina. Their findings do not encourage me to make use of anterior chamber implants using nylon loops to support the optical segment.

2. Also, it is difficult to establish an appropriate union between different materials; for example, a small hole is drilled in the side of the acrylic, and the nylon thread thrust into it. The entry hole is sealed off by thermocoagulation which can also degrade the parent polymer. This is not a very sound mechanical junction and over the years a number of agents might combine to dissolve this union, for example, minor trauma such as involved in cleaning the face and pressing lightly on the eye, the lytic action of the aqueous humor, and so forth. It only needs one of these junctions to become loose for the implant to disintegrate into multiple foreign bodies which would migrate within the eye. Removing these foreign bodies would be a most difficult surgical task, or an impossible one, and presumably the breaking up of such an implant into its components would in general mean the loss of the eye.

3. All the optical calculations are based on an implant occupying a predetermined position in the anterior chamber,* but with such an implant, supported only by loops, there is no possibility of designating where the implant will come to rest in the anterior cham-

ber, the location will depend upon the amount of tension exerted upon the nylon loops which will in turn depend on the diameter of the anterior chamber. Again, over the passage of many years one can envisage the nylon or tantalum loops losing their resilience, so that the implant sags backward into the pupillary area, or forwards so as to traumatize the posterior corneal surface, or inferiorly so as to rest in the angle below.

TYPE OF IMPLANT USED IN THIS RESEARCH

I decided at the commencement that previous work suggested that a one-piece all-acrylic implant was probably the safest to use. The manufacturers, Rayners Ltd., 160 New Bond Street, London, W.1., have therefore made me sets of implants for each case, each implant being a modified Strampelli type implant. The important differences from the type described by Strampelli are, firstly, that the anterior radius of curvature has been increased from 12 mm. to 14 mm., thus flattening the curve of the implant and carrying it away from the posterior corneal surface. The purpose of this modification was to try to reduce the incidence of endothelial corneal dystrophy. Secondly, the thickness of the haptic portion was standardized at 0.91 mm. Having done 100 cases with this type of implant, an eye containing one of these implants became available for pathologic study, as will be mentioned later, and having studied the specimen, I recommended reducing the thickness of the haptic portion to 0.50 mm. This has been done and

* 1.5 mm. \pm 0.5 mm. behind the posterior corneal surface and with its optical axis coinciding with the optical axis of the eye.

a further 20 cases have been treated using the thinner implants. Strampelli was informed of this modification by the manufacturers, but he stated that he did not wish to use these implants and did not wish to be associated with this new dimension, and the manufacturers have therefore called it the "Choyce anterior chamber implant," to distinguish it from Strampelli's original implant and from the thicker (0.91 mm.) implant used in my first 100 cases.

III. HOW SHOULD THE IMPLANT BE USED?

A. METHOD OF STERILIZATION OF THE IMPLANTS

The original method of sterilizing acrylic implants for intraocular use was described by Harold Ridley in the March, 1952, issue of the *British Journal of Ophthalmology*—30 minutes immersion in one-percent Cetavlon/Cetrimide, followed by repeated saline rinses. This method was used for the original Ridley lenticulus, but can also be used for anterior chamber implants.

This method of sterilization has its disadvantages since there is some evidence to show that some Cetrimide is adsorbed by the

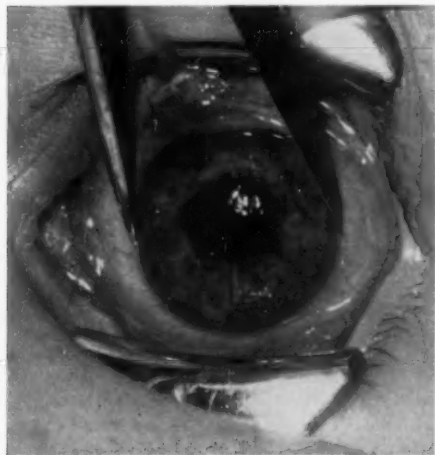


Fig. 3 (Choyce). Measurement of horizontal corneal diameter. (From *Philps Ophthalmic Operations*. (Edited by John Foster. London, Bailliere, Tindall and Cox, in press.)

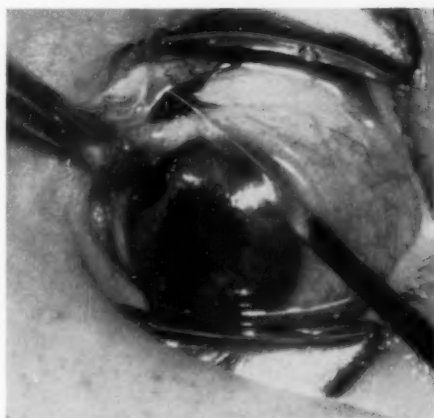


Fig. 4 (Choyce). Completion of section. (From *Philps Ophthalmic Operations*.)

implant, subsequently leaking into the eye and causing irritation. An alternative method of sterilization has therefore been developed by Frederick Ridley, as described by him in a paper "Safety requirements for acrylic implants" in the June, 1957, issue of the *British Journal of Ophthalmology*.

The implants are first polished and then sterilized in 10-percent NaOH and stored in 0.1-percent NaOH, and sent to the surgeon in this medium. The caustic soda is washed out with 0.5-percent sterile sodium bicarbonate at the time of operation.

For the first 30 cases in this series Cetrimide was used, and all subsequent cases have been sterilized using Frederick Ridley's caustic soda method. There is no doubt that the postoperative reaction has been much less severe and much less variable with the caustic soda method than with the Cetrimide method, and that the improvement in our results from this point of view cannot be due entirely to increasing experience with the surgical technique. It would, perhaps, have been more scientific to do a carefully controlled series using alternative methods of sterilization for alternate cases, but unfortunately the caustic soda method of sterilization did not become available until 30 cases had been treated, and since I was satis-



Fig. 5 (Choyce). Insertion of body of implant. (From *Philps Ophthalmic Operations*.)

fied that the caustic soda method was much safer, it did not seem justifiable to subject another later series of patients to the Cetri-mide technique when this had been shown to be less satisfactory than the new method.

Other methods which have been used are ultraviolet light, which again appears to cause a chemical change in the outer molecular layer of the implant and to degrade the parent polymer so that an irritant by-product is formed. Ethylene gas has been used in the United States, but this seems to be an unnecessarily expensive and cumbersome method of sterilizing the implants.

B. PREOPERATIVE MANAGEMENT OF THE CASES

Experience has shown that there are certain points which must receive careful attention if anterior chamber implant surgery is to be consistently successful. These factors are:

1. *Antecedent cataract surgery* together with any complications arising therefrom must have been satisfactorily completed and dealt with before anterior chamber implant surgery is carried out. This is one of the most important advances on the original Ridley method, which involved the insertion of an implant at the end of a major eye operation, namely, an extracapsular cataract

extraction with a peripheral iridectomy. By dealing first with the cataract surgery and only inserting the implant when the eye has been white and quiet for at least two to three months, it is possible to minimize the trauma inflicted upon the eye at each operative intervention.

2. *The iris.* Some form of superior iridectomy must be done, and if this has not been performed at the time of the original cataract surgery, then one should be performed by the ab externo method a week or so before the implant is inserted, for two reasons:

- a. If done at the same time as the implant is inserted there is a much greater risk of hemorrhage into the anterior chamber occurring during the operation or during the convalescent period. Blood in the anterior chamber tends to cloak the implant in a sheet of fibrin, which may take many months to absorb and may leave semipermanent strands of fibrin, which interfere with the visual result.

Organization of this clot would also increase the chances of angle blockage, and the onset of glaucoma from this cause.

- b. Technically, it is much more difficult to effect a satisfactory basal iridectomy through the incision used for insertion of the implant than it is to do a planned ab externo iridectomy superiorly as a single operative procedure.

The purpose of the iridectomy is twofold:

- (i) To ensure that there is proper circulation of aqueous between anterior and posterior segments, and

- (ii) To minimize the chances of the iris prolapsing in front of the implant. This will be referred to later in dealing with the management of the postoperative complications, but it can be stated here that such a prolapse will occlude a substantial part of the angle, and if it is not relieved glaucoma will supervene, the mechanism of its production being similar to that in iris bombé. This complication can be remedied by means of an ab externo iridectomy above or below, or both,

according to the site of the prolapse, but it is obviously better to avoid the necessity for this additional operative trauma if possible. Hence the value of an adequate superior basal (or complete) iridectomy before the implant is inserted.

3. There has been much discussion as to what sort of cataract surgery should precede anterior chamber implant insertion. I would say that it is not of any consequence. If the cataract surgery has been brought to a satisfactory conclusion, it makes no difference whether the posterior lens capsule has been totally removed or is present and intact, or present with a central gap. The presence of vitreous in the anterior chamber is not a contraindication to the insertion of an anterior chamber implant. It is, however, as well to know about this in advance because if the vitreous face has been broken, opening the anterior chamber at the commencement of the operation will liberate some vitreous.

The surgeon confronted, therefore, by a case of unioocular cataract and, having in mind the possibility of inserting an anterior chamber implant later, should treat the cataract on its merits as a cataract, and according to his usual practice.

The surgeon's attitude to the posterior lens capsule should be:

a. Perform whatever cataract operation he considers most suitable for the individual cataract case.

b. In children dense capsular remains should be removed by open operation and a complete iridectomy should be performed at the same time.

c. In adults, if the corrected visual acuity is good and there is an adequate view of the fundus, the posterior capsule is best left intact until implant surgery has been completed.

The following pathologic conditions absolutely contraindicate the use of an anterior chamber implant.

(i) Endothelial and/or epithelial dystrophy.

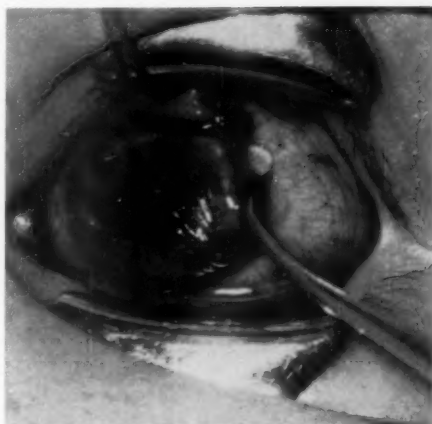


Fig. 6 (Choyce). Insertion of foot of implant. (From *Philps Ophthalmic Operations*.)

(ii) Aphakic glaucoma.

(iii) Aphakic retinal detachment.

(iv) Abnormally shallow anterior chamber.

(v) Recurrent iritis or iridocyclitis (other than cases of heterochromic cyclitis).

(vi) Extensive anterior synechias which resist surgical division.

(vii) Siderosis bulbi.

4. *Optical considerations.* The radius of curvature of the posterior surface of the optical portion of the implant is calculated for each individual case. The anterior chamber lens has an important advantage over the posterior chamber lens in this respect, because the operation for insertion of the anterior chamber implant is carried out after the patient has recovered from cataract surgery and it is therefore possible to calculate to within one diopter the spherical correction of the posterior surface of the implant to correct the refraction for infinity. At this stage it is also possible to make allowances if the refraction of the other eye exceeds $+1.0$ or -1.0 diopter. There is obviously no point in replacing one variety of anisometropia with another and if the patient requires $+4.0D$. sph. or $-6.0D$. sph. to correct the phakic eye complete visual comfort will only be achieved by arranging for the

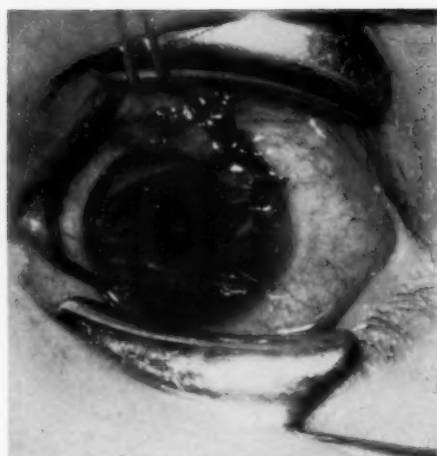


Fig. 7 (Choyce). Suture tied. Section closed.
(From *Philps Ophthalmic Operations*.)

aphakic eye to require a comparable spherical correction after the implant has been inserted.

These calculations are based on the positioning of the major sphere in the trial frame at 10 mm. in front of the anterior surface of the cornea. Therefore, when the surgeon refracts the aphakic eye, he must record the back vertex distance, and forward this measurement with the spherocylindrical combination to the manufacturers. By consulting tables, they can adjust the spherical component to a back vertex distance of 10 mm.

No attempt has so far been made to anticipate or to correct the cylindrical error in any given case. There are two reasons for this:

a. It is very difficult to predict the residual cylindrical correction in any given case.

b. It is a complicated and expensive business to produce a cylindrical correction on an acrylic implant. In general, the residual cylinder required is usually found to be a minus cylinder, the axis of which varies between 30 and 150 degrees, that is, 30 degrees on either side of the horizontal. In dioptric power it has not exceeded -4.5 diopters. Table 6 summarizes the residual cylindrical

correction in this group of cases, the average being -2.47D. cyl.

The surgeon's procedure is, therefore, as follows:

Having performed the cataract surgery, he should wait approximately six weeks for the eye to settle down. A careful refraction is then carried out and the spherocylindrical correction with a record of the back vertex distance* is forwarded to the manufacturers. At this stage the horizontal corneal diameter should also be measured, because it has been found that in the majority of cases the correct length of implant to insert is the horizontal corneal diameter plus one mm. Less than this means that there is a danger of the implant being too small and moving about inside the anterior chamber. If this occurs, it will set up irritation of the ciliary body and the iris; traumatic iridocyclitis and secondary glaucoma will ensue. If the implant is longer than this it will be found very difficult to insert and, when inserted, it will lead to unnecessary distortion of the eye in the 3 to 9-o'clock meridian.

Relationship of horizontal corneal diameter to age

It has been suggested that it is unwise to insert anterior chamber implants of fixed length into the growing eye of a young child because of the theoretical possibility that an implant which was a snug fit at the age of two or three years would be too short for the eye as the child became older. It would become loose and move about in the anterior chamber traumatizing the corneal endothelium and irritating the iris and ciliary body and setting up iridocyclitis and secondary glaucoma. However, Wolff (*The Anatomy of the Eye and Orbit*, third edition, page 376), states that "the cornea reaches adult size at about two years or earlier and that later growth affects mainly the posterior segment."

*Back vertex distance is the distance in mm. between the posterior surface of major sphere in trial frame and anterior surface of cornea.

TABLE 1
HORIZONTAL CORNEAL DIAMETERS

Horizontal Corneal Diameter (mm.)	Age (yr.)	Totals
10.5	70, 65, 14, 26, 77, 64, 54, 15.	8
11.0	60, 50, 2, 11, 64, 52, 58, 50, 73, 52, 64, 56, 73, 64.	14
11.5	59, 76, 63, 70, 3, 50, 60, 62, 61, 48, 47, 4, 63, 78, 73, 56, 3, 75, 63, 2, 12, 68, 38, 38, 78, 59, 76, 79, 40, 66, 77, 68, 72, 70, 31, 61, 81, 74.	38
12.0	47, 36, 11, 41, 8, 9, 3, 40, 58, 73, 60, 15, 45, 63, 63, 78, 3, 70, 78, 45, 60, 53, 20, 11, 69, 60, 79, 68, 69, 55, 32, 62, 68, 47, 74, 65.	36
12.5	6, 44, 66, 78, 65, 26, 12, 50, 48, 64, 57, 11, 25, 33, 20.	15
TOTAL		111

Table 1 gives the horizontal corneal diameters to the nearest 0.5 mm. and the ages in years of the 111 cases studied herein.

Table 2 correlates these diameters in the 0-4 age group, 5-14, 15-24, and so forth age groups.

Table 3 correlates these age groups with the mean corneal diameter.

These figures support Wolff's statement that the cornea and, therefore, the horizontal corneal diameter reaches adult size at the age of two years or earlier. If there is a tendency shown by these tables and charts,

TABLE 2
CORRELATION OF HORIZONTAL CORNEAL DIAMETERS

Age (yr.)	10.5 (mm.)	11.0 (mm.)	11.5 (mm.)	12.0 (mm.)	12.5 (mm.)	Totals
0-4	0	1	4	2	0	7
5-14	1	1	1	4	3	10
15-24	1	0	0	2	1	4
25-34	1	0	1	1	3	6
35-44	0	0	3	3	1	7
45-54	1	4	3	5	2	15
55-64	1	6	10	8	2	27
65-74	2	2	8	8	2	22
75-84	1	0	8	3	1	13
	8	14	38	36	15	111



Fig. 8 (Choyce). Unilateral traumatic aphakia in a woman aged 46 years. The aphakia was caused by concussion injury (shuttlecock) at the age of 15 years. It was corrected by an all-acrylic anterior chamber implant, with 20/20 visual acuity and full binocular single vision. (Photographed 18 months after insertion of the implant.)

it is that these corneal diameters are greatest in the young but this trend is not statistically significant. It is clear, however, that there is no more danger in inserting anterior chamber implants in the two to five years age group than there is at any other age. The youngest patient in this series received his implant at the age of two years and three months. That was two years ago and the implant is still a nice tight fit and the eye white and quiet and the cornea bright and clear.

5. The stage has now been reached where the patient can be admitted to hospital for insertion of the anterior chamber implant. On admission, routine physical examination is carried out, with special reference to hy-

TABLE 3
CORRELATION OF AGE GROUPS WITH MEAN CORNEAL DIAMETER

Age (yr.)	Mean Corneal Diameter 3-9 o/c (mm.)
0-4	11.57
5-14	11.85
15-24	11.75
25-34	11.91
35-44	11.86
45-54	11.60
55-64	11.57
65-74	11.64
75-84	11.62

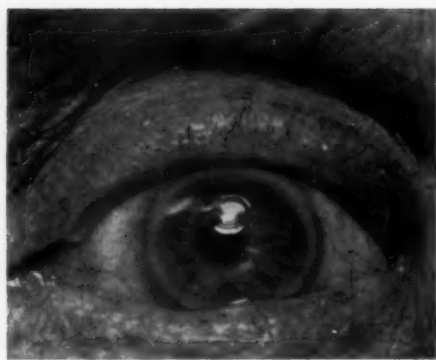


Fig. 9 (Choyce). Uniocular senile cataract corrected by thin Choyce anterior chamber implant.

pertension and diabetes mellitus. If the blood pressure is raised, and/or if diabetes is present, special steps must be taken to reduce the incidence of bleeding at the time of operation. Adrenoxyl is given in the following dosage: 5.0 mg. b.d. for two days preoperatively and 0.75 mg. intramuscularly one hour preoperatively.

The eyes should also be carefully examined to make sure that there have been no changes since the order for the implant was transmitted to the manufacturers. The refraction should be carefully checked and ophthalmoscopy carried out, because it does sometimes happen that some complication, such as aphakic retinal detachment, has occurred since the anterior chamber implant was ordered.

Gonioscopy should also be carried out routinely and, if a substantial part of the angle is closed by peripheral anterior synechias, the insertion of the anterior chamber implant should be postponed until measures have been undertaken to reopen as much of the angle as possible. Cyclodialysis is probably the most effective procedure; if this fails, an ab externo peripheral iridectomy should be performed.

The importance of paying careful attention to the state of the angle lies in the fact that insertion of an implant into an eye where, say, 50 percent of the angle is oc-

cluded would very likely result in a tendency for the iris to come forward and prolapse in front of the implant, usually from below, sometimes from above, and sometimes from below and above.

Once this occurs there is massive occlusion of the angle, and a marked tendency for the intraocular pressure to rise. This complication is particularly likely to occur after intracapsular extraction, especially if there has been delay in reformation of the anterior chamber following the cataract surgery.

The eye is prepared as for any other intraocular operation; the lashes should be cut and the conjunctival sacs irrigated every hour or so with antibiotic drops. At the Southend Hospital we never culture the conjunctival sac preoperatively; we prefer to rely on the clinical appearance of the eye and the routine use of these antibiotic drops. While this may not be the generally accepted practice, the fact remains that none of the cases operated upon in this series developed an infected eye. The pupil should be kept miotic with two-percent Pilocarpine drops (four hourly) for 24 hours before operation and immediately before the operation. The purpose of this is again to facilitate the introduction of the implant and to discourage the iris from undergoing intraocular anterior prolapse.

C. ANESTHESIA

The operation can be carried out under either local or general anesthesia. In the case of a nervous patient or a child, general anesthesia is obviously indicated. This must be deep, with appropriate endotracheal intubation, and any anesthetic agents which tend to lower the intraocular pressure are desirable.

Dr. J. Alfred Lee, senior anesthetist to the Southend Group of Hospitals, has contributed the following note on anesthesia. The methods he employs as of today are:

1. For the very small child in whom intravenous technique is difficult, rectal pentothal, gas oxygen and trilene, which is

followed by blind nasal intubation.

2. For older children, rectal pentothal (1.0 ml. of 2.5-percent solution per lb. of body weight), followed by pentothal intravenously and a small dose of flaxedil, followed by succinylcholine followed by intubation and gas oxygen; pethidine (Demerol in the United States) may be given to control cough, and very occasionally trilene in addition.

3. For the fit adult, premedication is Demerol 50-100 mg. with promethazine (Phenergan) 25-50 mg. Induction by a slow drip of chlorpromazine (Largactil) 50-100 mg. promethazine 50-100 mg. and Demerol 50-100 mg. in 500 ml. of dextrose. Then pentothal, flaxedil and succinylcholine and oral intubation with a large tube and gas oxygen maintenance. These fit patients may receive instead, gas oxygen and fluothane through a large intratracheal tube, preceded by a pentothal induction.

4. For old, feeble, patients, we may use either the techniques just outlined, perhaps with general reduction of dosage, or it may be preferable to use pentothal, gas oxygen and trilene, perhaps using Demerol too.

It would seem that succinylcholine (scoline, anectine in the United States) will raise the intraocular pressure if the usual muscular fasciculations are allowed to occur. This effect can be abolished or greatly reduced if before the injection of the scoline, a small dose (20 mg.) of flaxedil or 3.0 mg. of d-tubocurare is injected.

If the operation is carried out under local anesthesia, premedication is with Largactil and Oblivon, in doses adjusted to the age and physical condition of the patient; Amethocaine (0.5 percent) and Pilocarpine (one percent) drops are used; adrenalin drops are contraindicated because of their tendency to cause dilatation of the pupil. There must be facial akinesia and a retrobulbar injection of about 1.25 ml. of four-percent Procaine should be given, either from above or below. The hypotonic effect of this injection is enhanced if firm



Fig. 10 (Choyce). Section of anterior segment of eye containing anterior chamber implant (thick variety, 0.91 mm.), showing space taken up by the implant. (Ashton, N., and Choyce, D. P.: *Brit. J. Ophth.*, 43: 577, 1959.)

pressure is made on the eyeball through the closed lids for one to two minutes after the injection has been given. If a retrobulbar hemorrhage occurs following the injection the operation, of course, has to be abandoned, another attempt being made a few weeks later.

D. PROCEDURE AT OPERATION

Insertion of anterior chamber implant. The purpose of this operation is to insert an implant suitable for the individual case; of a correct length so that its optical axis coincides with the optical axis of the eye; and to effect this with the minimum of trauma to the eye.

Adequate exposure is provided by an ordinary lid speculum; lid sutures are not sufficient. A superior rectus suture is inserted and the horizontal corneal diameter is measured once more. This should be the same as when the diameter was measured before the implants were ordered.

The canister containing the sterilized implants is then opened and the 0.1-percent caustic soda poured off. The canister is half filled with sterile sodium bicarbonate and the implants gently irrigated for about a minute. This solution is then poured off and replaced by more sodium bicarbonate and the lid secured into place.

The container is then put the right way up and the lid is then unscrewed; the device which holds the implants in position is removed and the implant of correct length (= horizontal corneal diameter ± 1.0 mm.) gently picked out of the container and placed

on the metal ruler so that its length can be checked. The length having been checked the implant is then placed in a watch glass filled with normal saline to await insertion into the eye.

Usually these maneuvers are carried out by the assistant while the surgeon makes his incision into the eye. This incision should be made from the 7- to the 11 o'clock position in the right eye and from the 5- to the 1-o'clock position in the left eye. The use of a narrow-bladed Graefe knife for this purpose is preferable to the use of a keratome for three reasons:

1. Much less force is required to make the incision.

2. Fewer epithelial cells are carried into the anterior chamber so that epithelization of the anterior chamber is less likely to occur.

3. It is possible with a knife to avoid the pupillary area which is important if the vitreous face is protruding, mushroomwise, through the pupil into the anterior chamber. If a keratome is used the vitreous face will be pricked and vitreous will escape from the eye.

Both puncture and counterpuncture should be just, and only just, on the corneal side of the limbus. No conjunctival flap should be raised. There should be a shelf of corneal tissue 0.5 to 1.0 mm. on the corneal side of the limbus. Cutting this section is usually quite easy if the surgeon is ambidextrous and can use the right hand for the right eye and the left hand for the left eye. The other hand should steady the eyeball by grasping and lifting the insertion of the superior rectus.

This maneuver can, however, be quite difficult if the eye is unusually small and the socket unusually deep. In such a case the surgeon must be content to make a slightly smaller incision and to enlarge it as necessary with Tudor-Thomas corneal scissors.

If vitreous is present in the anterior chamber and the vitreous face has been broken, there will inevitably be an escape of

some vitreous on cutting this section. Provided loss is confined to modest dimensions it does not adversely affect completion of the operation or damage the prognosis of that particular case.

Having cut the section the surgeon should satisfy himself, by introducing an iris repositor, that the incision is sufficiently wide to permit the introduction of the implant. At this stage it may occasionally be necessary to introduce de Wecker's scissors and divide residual anterior synechias which would otherwise prevent introduction of the implant.

In general, however, maneuvers such as division of anterior synechias or iridectomy should have been dealt with by preliminary operations so as to keep to a minimum the trauma inflicted on the eye when the implant itself is introduced.

Next the surgeon picks up the implant at about its middle with the Ridley forceps, using the left hand for a right eye and the right hand for a left eye, and then grips the feet of the implant with the Barraquer forceps (which are more steeply angled) with the other hand.

The Ridley forceps are taken off and the surgeon introduces the implant through the incision in the anterior chamber using the right hand for the right eye and the left hand for the left eye. It is prudent to point the tip of the implant slightly downward, thus taking it away from the contracted pupil and keeping the tip clear of the nasal part of the pupil.

As soon as the implant has passed toward the nasal limbus, the surgeon's assistant should place the tip of a repositor between the feet of the implant so as to steady it while the surgeon takes off the Barraquer forceps. These are sometimes inclined to stick to the feet of the implant and, if it is not steadied in this fashion, the surgeon may find it rather difficult to take the forceps off.

Having removed the forceps all that remains is to introduce the two feet into the angle of the anterior chamber. This is best achieved by gently catching the outer (scler-



Fig. 11. Old traumatic cataract.

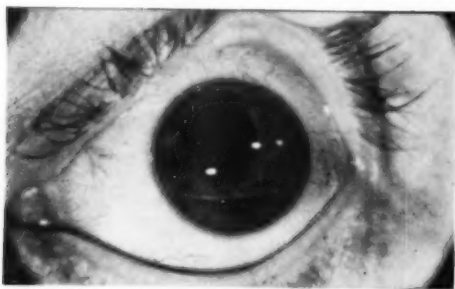
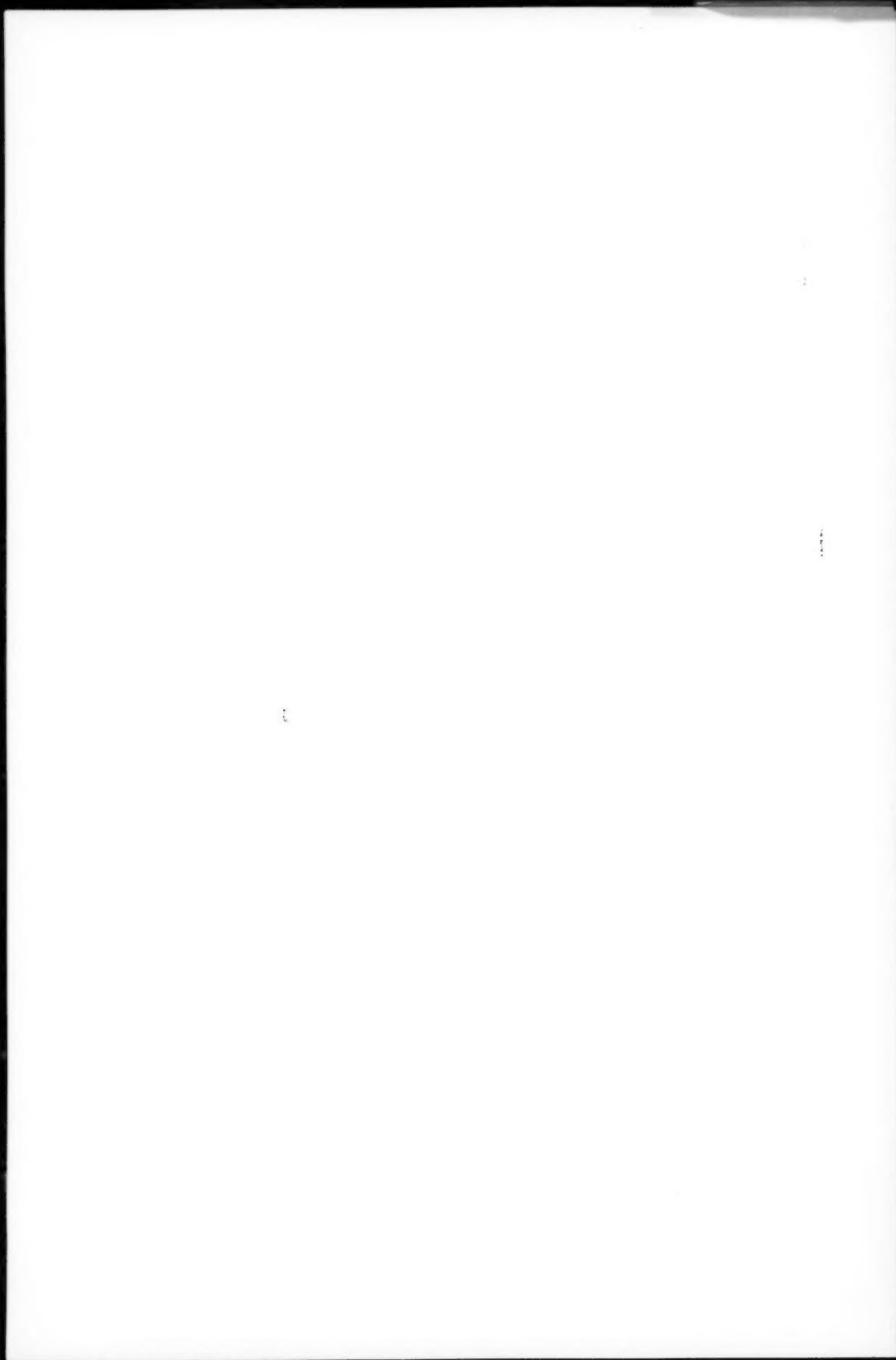


Fig. 12. Old traumatic aphakia.

Figs. 11 and 12 (Choyce). The correction of unocular aphakia by means of all-acrylic anterior chamber implants.



ral) lip of the incision with fine-toothed forceps and retracting it outward and slightly upward while pressing gently on one foot of the implant with the tip of an iris reposer. Usually the foot gives a little plop as it tips over the edge and takes up its position in the angle.

The maneuver is repeated for the other foot of the implant, and it is usually quite obvious to the surgeon when the implant is in fact safely inside the anterior chamber. A fresh reposer is used to slide along the length of the incision, making sure that the corneal part of the incision is not turned in.

One suture is inserted now through the middle of the incision corresponding to the space between the feet of the implant. I use the finest Barraquer corneal needle with the finest black silk. The first hitch is a double hitch and then I complete the suture with two single hitches. This suture should not be tied tightly because otherwise it will cut through the edges of the cornea.

The anterior chamber is now gently irrigated with normal saline at 37°C.; it does no harm to inject a little sterile air after this but this is not really necessary. Pilocarpine (one-percent drops) is instilled from time to time during the course of the operation so as to maintain miosis. Bleeding should not occur during this operation; if any traces of blood should find their way into the anterior chamber they should be removed so far as possible by gentle irrigation with saline.

The speculum and the superior rectus stitch should now be removed, and the eye again carefully inspected because removing the speculum sometimes moves the implant up or down by about one mm. which, of course, means that its optical axis no longer coincides with the optical axis of the eye. The surgeon should be satisfied that the implant is exactly in the midhorizontal plane before closing the lids. If not quite central, it can easily be moved into this plane by pressing on its upper or lower edges through the cornea by iris reposers. However, the implant rapidly becomes embedded in its po-

sition and it is not possible to push it into a more favorable position after the passage of 24 hours. Pilocarpine (two-percent drops) is instilled and polyfax ointment introduced in the conjunctival sac; a square of sterile vaseline gauze is laid over the closed lids; a pad is applied to each eye and a Moorfields bandage protects them both.

The crux of the operation is to insure that the implant fits snugly. If it is too short, it will move about the anterior chamber, irritating the iris and ciliary body and setting up secondary glaucoma. If it is too long, it is very difficult to insert and subjects the eye to unnecessary deformation in the horizontal axis. While the rule of "horizontal corneal diameter + 1.0 mm." is generally correct, it does occasionally happen that the surgeon is left with a strong impression that the implant inserted is either too long or too short. In such an event he must not hesitate to remove this implant and insert another, 0.5 mm. longer or shorter, as his judgment suggests. As his experience of the operation increases, however, he will have to do this less and less often.

E. POSTOPERATIVE CARE

Immediately the operation is completed the patient is given an intramuscular injection of penidural as a prophylactic against infection. If patients are penicillin-sensitive, they are given some other broad-spectrum antibiotic systemically, such as achromycin. Happily no cases in this series developed postoperative infection but it is felt that the use of some antibiotic of this nature is wise. Some pain is usually experienced when the patients recover from the anesthesia and this is usually relieved by codeine tablets.

Twenty-four hours after operation the first dressing is performed. Often the cornea is somewhat cloudy due to edema of the corneal endothelium and Descemet's membrane. There may be some chemosis of the conjunctiva. The eyelids are gently cleaned, neomycin ointment instilled into the conjunctival sac, the eye is repadded and the

other eye left uncovered. This treatment is repeated on the second day.

On the third day the corneal suture is removed, under local anesthesia in the case of an adult and under general anesthesia in the case of a child. At the same time a subconjunctival injection of 20 mg. of cortisone is given. The following day the eyepad can be discarded and dark glasses are worn.

Mydriatics are never used at this early stage in convalescence because of the danger of precipitating anterior prolapse of the iris before the anterior chamber has properly reformed.

The patients are usually ready for discharge five to six days after insertion of the implant. They are discharged with a supply of 2.5-percent oculentum hydrocortisone for use twice daily. They wear dark glasses out of doors but not indoors. They are next seen by the surgeon a week after discharge. The hydrocortisone ointment is continued until the eye is white which may take several weeks, often as much as six to eight weeks.

No attention is paid to the visual acuity or refraction until at least two months have elapsed but the patients usually volunteer the information that the vision is steadily improving in the operated eye.

In the case of a child under the age of 10 years the affected eye will almost certainly be amblyopic to some degree and for these cases it is essential that total occlusion of the good eye be commenced as soon as the child can open the operated eye and can keep it open in all but the strongest light. This stage is usually reached about two to three weeks after the operation has been carried out and this occlusion should be maintained for at least two months.

None of the patients in this series have complained of diplopia following the operation. At the end of two months refraction is carried out and, if the standard vision achieved approximates that expected, distance and reading glasses (or bifocals) are prescribed. If the refraction does not appear to have reached a stable level, refraction is repeated a month later. It should be possible,

however, to provide the patient with a more or less permanent prescription for glasses by the end of three months after the operation.

At each postoperative visit the surgeon must satisfy himself that the intraocular pressure is within normal limits and, if in doubt, Diamox must be started or continued.

Following prescription of the final correction the patients should be seen again three months later and then six months later and then at yearly intervals. They can lead a normal life but in the case of children or athletically-minded adults, they should be carefully warned to avoid occupations or sports in which they might be struck violently in the affected eye. Apart from that there are no restrictions on their activities. I have one patient working in an overseas police force, another as an officer in the Merchant Navy, and another in a foundry.

Some patients find that, if they wash their faces unduly vigorously and press upon the affected eye, they get a twinge of pain, presumably because they press the implant back onto the iris; at the same time the posterior corneal surface comes into contact with the anterior surface of the implant so that the patients should be warned to be careful concerning this point. They usually find this out for themselves.

IV. WHAT COMPLICATIONS MAY BE ENCOUNTERED?

These can be considered under the following headings:

1. Within one week of operation.
2. From one week to three months after operation.
3. From three months to three years after operation.

1. WITHIN ONE WEEK

a. *Edema of corneal endothelium and Descemet's membrane* causing striate keratitis is almost always found at the first dressing. This should gradually lessen day by day so that by the time the patient is discharged from hospital the cornea should be approaching its normal translucency.

b. *Prolapse of iris in front of the implant.* This should not occur if an adequate basal iridectomy has been performed prior to the insertion of the implant, if the pupil has been properly miotic before operation, and if the surgical technique has been gentle and skilful. It is particularly likely to occur if the anterior chamber is unusually shallow or if there are extensive peripheral anterior synechias.

The mechanism of its production seems to be that there is, within the first 24 hours after operation, an exudative reaction behind the iris which forces it forward in front of the lower and sometimes the upper border of the implant, as in the condition of iris bombé.

First the pupil margin becomes prolapsed in this way. It is likely to be permanent and, since a large area of angle will be occluded by the iris, secondary glaucoma is inevitable (as in iris bombé). Therefore the condition must be remedied. Medical measures are tried first. One-percent eserine drops should be instilled every hour. Diamox (250 mg. t.d.s.) and corticosteroids should be given by mouth. If the condition is still present after three days of this regimen, an ab externo iridectomy must be carried out. This is not especially difficult and, on making the incision at the limbus, the iris usually presents spontaneously and that amount of iris which presents should be abscised and the conjunctival flap replaced. Sometimes this additional iridectomy is found to be complete and sometimes the sphincter is preserved.

Anterior prolapse of the iris has occurred in eight cases. In seven it was inferiorly and in one it was both superiorly and inferiorly. The medical measures just described were successful in reducing the prolapse in three cases; in four, an inferior ab externo iridectomy had to be performed; and in one inferior and superior ab externo iridectomies had to be carried out. The final results in these eight cases were quite satisfactory.

c. *Iritis* leading to secondary glaucoma has occurred in six cases within a few days

of operation. The use of Diamox and systemic corticosteroids caused the condition to subside within three to four days and, apart from a slightly longer stay in hospital, the convalescence of these patients was no different from that of the others in this series.

d. *Hemorrhage* into the anterior chamber has occurred from time to time but in only two cases has it been troublesome. In both these cases an iridectomy was performed at the time the implant was inserted and that is way I recommend that iridectomy should be performed previous to the operation for insertion of the implant. In these two cases blood clots and fibrin covered the implant's anterior and posterior surfaces and took three to four months to absorb.

In one of these cases there were fibrin strands reaching up from the inferior angle to the implant and it was most interesting to observe the efforts of fibroblasts or epithelial cells to fill this space, as though they were conducting an experiment in tissue culture! Fortunately they were not successful and eventually they regressed but this is obviously a complication to be avoided if possible.

2. FROM ONE WEEK TO THREE MONTHS

a. *Endothelial corneal dystrophy.* There have been five cases of this complication in this series of 111 cases.

The second and fifth cases (of the 111) both developed corneal dystrophy although the operations went smoothly and the posterior corneal surface was not unduly traumatized. The anterior chambers reformed quickly and it was felt that the dystrophy was due to chemical trauma caused by the Cetavlon method of sterilization of the implants. After the first 30 cases, the method of sterilization was changed to the caustic-soda technique described by Frederick Ridley and there have been no further cases of corneal dystrophy which could be ascribed to this cause.

The other three cases were due to inserting implants which were too short and which moved round the anterior chambers

traumatizing the corneal endothelium, as well as the ciliary body and iris. These implants were removed and replaced with implants between either 1.0 or 1.5 mm. longer but in two cases the dystrophy progressed so that the vision is only hand movements. In one case, however, the dystrophy has partially regressed so that the vision has improved to 20/200.

A sixth case had endothelial corneal dystrophy before the operation was performed. The patient was warned that introduction of an anterior chamber implant would almost certainly make the dystrophy worse but he still asked for the operation to be carried out. As anticipated, the dystrophy which had affected about one quarter of the cornea extended to cover three quarters of it and his vision also is only hand movements. However, the eye is quite comfortable and the patient expresses himself quite satisfied with this result. Previously his eye had been a source of great trouble to him and now it is symptom free.

b. *Iritis*. Two diabetic patients developed a troublesome iritis at this stage with a slight increase in intraocular pressure. Administration of systemic corticosteroids dealt with the acute phase but the patients have been kept on Diamox (250 mg.b.d.) subsequently as a precaution.

3. FROM THREE MONTHS TO THREE YEARS

There have been remarkably few complications of a delayed nature. Nearly all the difficulties have been concentrated in the first three months after operation.

There have been two cases of iritis occurring one year later, leading to secondary glaucoma for which the implant was removed. The implant was also removed from from a third case which had siderosis bulbi and aphakic glaucoma before the implant was inserted. The tension gradually rose again after the operation and 18 months later there was a certain amount of pain so the implant was removed. These three cases have comfortable aphakic eyes with some vision.

Two of the cases of heterochromic cyclitis went through a phase when their cyclitis was unusually active but it responded to the usual medical measures and this can hardly be regarded as a complication of implant surgery.

SUMMARY OF COMPLICATIONS

Of eight cases of anterior, that is, intraocular, prolapse of the iris, three responded to medical measures and the final visual result was satisfactory. Of five cases of endothelial corneal dystrophy, two were due to the Cetavlon method of sterilizing the implants and three were due to inserting too short an implant.

Five implants were subsequently removed because of iritis leading to secondary glaucoma. Two of these were in diabetics and in two the implant inserted had been too short and had set up secondary glaucoma. In one case, siderosis bulbi and aphakic glaucoma were present before the implant was inserted.

It should be noted at this stage that certain complications that might have been expected have not in fact been encountered, such as: (a) infection of the eye, (b) sympathetic irritation or sympathetic ophthalmia, and (c) aphakic retinal detachment. None of these complications have so far arisen.

CAUSES OF CATARACT OR APHAKIA IN 111 CONSECUTIVE CASES

Table 4 summarizes the causes of cataract or aphakia in the 111 cases studied.

a. *By congenital cataract* is meant cases in which a uniocular cataract has been present since birth though in some of them a few years elapsed before the condition was recognized. Therefore, a varying degree of amblyopia was superimposed upon the visual difficulty caused by the cataract, the degree of amblyopia depending upon the density of the cataract and the number of years that elapsed before it was treated.

TABLE 4
CAUSES OF CATARACT OR APHAKIA

Causes	No. of Cases
Congenital cataract	7
Traumatic cataract	35
Senile cataract in the 51 yr. & over age group	45
"Senile" cataract in the 20-50 yr. age group	9
Heterochromic cyclitis	11
Complicated cataract from iritis with secondary glaucoma	4
TOTAL	111

Where the affected eye was markedly smaller than its fellow or where other congenital defects were apparent, no treatment was attempted. In the seven cases featured in this series, however, the eyes were of the same size and cataract surgery revealed no obvious lesions of the vitreous, choroid, retina or optic nerve.

b. *Traumatic cataract.* In this series, 23 cases were the result of perforating injury; nine cases were due to concussion alone; three were due to concussion plus subluxation or dislocation of the lens; 11 were recent injuries, that is, the implant was inserted within two years of the trauma; in the remaining 24 cases, the implant was inserted more than two years after the original injury. These 35 cases formed a most interesting group.

c. *Senile cataract in the 51-years and over age group.* In this group the lens of the other eye was either entirely clear or, if present, the opacities were few in number, confined to the periphery of the lens, non-progressive or only very slowly progressive, and did not interfere with the vision of the eye.

d. *"Senile" cataract in the 20- to 50-years age group.* It would appear somewhat unsatisfactory to describe these nine cases as senile but morphologically their cataracts were indistinguishable from the usual forms of senile cataract.

Possibly some of these cataracts had a congenital basis upon which senile changes were superimposed but by the time they

were examined by me it was not possible to differentiate the two forms.

e. *Heterochromic cyclitis.* This syndrome which was originally described by Fuchs is, nevertheless, little understood at the present time and there are those who question its right to be regarded as a separate disease entity (Woods, *Am. J. Ophth.*, 45: 251-268, 1958). Nevertheless, in this series there are 11 cases in which one eye was entirely normal and the other was the seat of a complicated cataract associated with heterochromia and atrophy of the iris, a quiet cyclitis as shown by fine deposits of keratic precipitates, and no posterior synechias. The cyclitis varied in extent, being barely discernible in some cases and very evident in others. None of these cases had reached the stage of glaucoma at the time surgical intervention was carried out.

f. *Complicated cataract from iritis with secondary glaucoma.* Two of these cases were the result of infection of a pre-existing trephining bleb and the other two were the result of an infected corneal ulcer.

V. WHAT PERCENTAGE OF SUCCESS CAN BE EXPECTED?

In my hands, intraocular surgery is a discipline always dangerous, often difficult, and frequently disappointing. As seen against that background the short answer to this question is that the percentage of success is very satisfactory, and has exceeded my most optimistic calculations. It can be considered in detail under the headings of visual acuity, binocular function, and psychologic benefit.

A. VISUAL ACUITY

These cases have varied as to the level of visual acuity to be expected; in some the corrected aphakic visual acuity had been reduced either by organic changes, such as old commotio retinae, or corneal scarring, or by amblyopia ex anopsia if the injury had occurred before the age of 10 years. The younger the age at which the cataract ap-

TABLE 5
CORRECTED VISUAL ACUITY BEFORE AND AFTER
INSERTION OF ANTERIOR CHAMBER IMPLANT

Visual Acuity	Before	After
20/20	19	32
20/30	52	31
20/40	12	10
20/70	8	8
20/100	4	7
20/200	4	4
<20/200	12	19
TOTAL	111	111

pears, the denser the degree of amblyopia. Clearly it is not to be expected that introduction of a correcting lens into the eye could improve upon the antecedent vision obtained with a suitable aphakic correction. It is a fact that 60 percent of these patients see 20/30 or better, but such a statement is of little value for the reason just given. Table 5 shows the corrected visual acuity before and after insertion of the anterior chamber implant. Chart 1 shows that in general the visual acuity target aimed at has been achieved.

In fact, 32 patients saw 20/20 or better after insertion of the implant, whereas only

19 saw 20/20 or better before the implant was inserted. At the other end of Table 5 there has been a slight increase following insertion of the implant, 19 as against 12 whose visual function is less than 20/200. This figure includes the five cases already referred to where for one reason or another the implant has subsequently been removed, and their unaided vision is about the usual for uncorrected aphakia. There are no totally blind eyes in this series.

Many of these patients require some form of residual spherocylindrical correction before achieving this level of visual acuity. The spherical component of this final correction has been within one diopter of the target in 90 percent of the cases, which speaks very highly for the accuracy of the mathematical calculations made by the team concerned. In the remaining 10 percent, the residual spherical correction varied between +2.0D. sph. and -3.0D. sph., and I cannot account for this degree of aberration. The cylindrical correction required is invariably a minus cylinder with the axis within 30 degrees of the horizontal. Table 6 gives the full details.

By residual cylindrical correction is meant

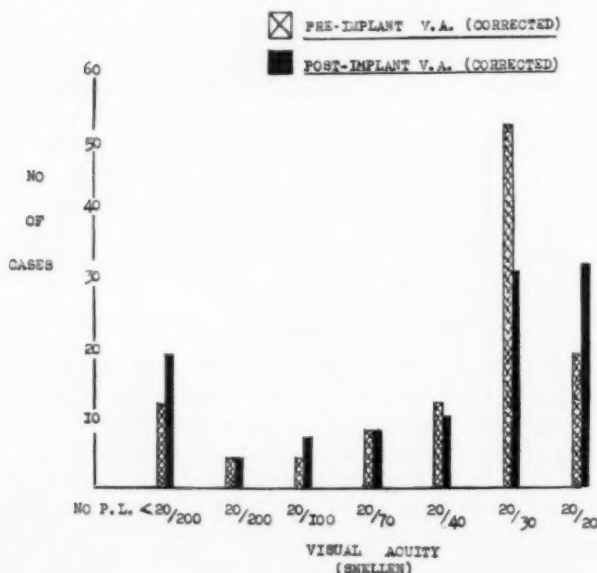


Chart 1 (Choyce). Showing visual acuity before and after insertion of anterior chamber implants in 111 cases.

TABLE 6
RESIDUAL CYLINDRICAL CORRECTION

Net	Gross	Net	Gross	Net	Gross
MINUS	MINUS	MINUS	MINUS	MINUS	MINUS
1.5	2.5	0	0	4	2
2	1.25	3	4	4	4.5
4	3	3.5	5.5	1	3
4	2.5	0.75	2.75	1.75	2.25
1.75	0.75	1.5	3	3	4.45
3	2.25	1.5	4	0	0
4.5	4	3.5	3.5	3	4
0.75	1.75	3	5.5	3	4.5
2	0.5	3	2	2	3
3.5	3.5	2.5	4	4	1
3	3	3	4	2	0.5
2.5	1.5	3	4.25	0.75	1.75
1.75	1.75	3	2	3	3.5
3	3	2.5	4	3.5	4.5
2	1.75	3	2.25	1.75	3.25
3.5	2.75	2.5	1.75	2.25	2.75
4.5	3.75	1.5	2.5	0.75	1.75
1.5	0.5	2.25	2.75	2.25	3.75
1.5	1.5	2	2	4.5	3
2.5	3.75	3.5	1.5	2	1
1.5	3.5	2.5	3	1	3
4	3.25	3	7	3.5	4.5
3.5	6	0	2	1.75	0.75
2	3	3.5	4	0.75	1.75
0	0	2	2	3.5	4.25
1.25	0.75	3	4	2	0.5
3.5	4.25	4	3	4	5

the final cylindrical correction incorporated in the glasses ordered for the patient, but since this is often added to a plus or sometimes a minus cylinder, axis roughly horizontal, the result of antecedent cataract surgery, the true or gross cylindrical correction is obtained by adding the final to the antecedent cylindrical corrections.

Thus, if a patient requires +11D. sph. \ominus +1.5D. cyl. ax. 180° before insertion of the implant, and the final correction is 0.0D. sph. \ominus -1.0D. cyl. ax. 180°, the net cylindrical correction is -1.0D. cyl., but the gross cylindrical correction is -2.5D. cyl. The average net cylindrical correction in this first 111 cases is -2.47D. cyl., axis horizontal. The average gross cylindrical correction in the same series is -2.79D. cyl. Which confirms the usual tendency of a cataract operation to leave the patient requiring a plus cylinder, axis roughly horizontal.

I have noticed a tendency for the residual cylindrical correction to become less in my most recent cases, which suggests that, as

the surgeon's experience increases and his surgical technique improves, the scarring of the cornea is less dense and the residual astigmatism correspondingly less.

I am not quite sure why these patients develop this residual astigmatism. It must be due in part to the temporal corneal incision which would, of course, impart an astigmatism the opposite of that produced by the usual cataract incision at right angles to the one used for the insertion of an implant. It may also be caused in part by inserting an implant which is deliberately made a somewhat tight fit and which therefore puts the eye slightly on the stretch by perhaps one mm. in the horizontal plane.

These patients, of course, also require an additional correction for near, varying between +2.5D. sph. and +3.5D. sph. In presbyopes, bifocal glasses have usually been prescribed, but children and young adults seem to be happier with two separate pairs of glasses, one for distance and one for near.

B. BINOCULAR FUNCTION

By binocular function I mean full binocular single vision and full stereopsis as elicited by the following tests:

1. *Visual acuity.* Good enough in both eyes to permit binocular single vision.

2. *Cover test.* No deviation or esophoria with recovery to binocular single vision for near and distance.

3. *Worth's lights.* Four for near and distance.

4. *Synoptophore.* (a) Presence of simultaneous macular perception with normal retinal correspondence; (b) fusion must be present with a range of adduction and abduction (I have found that the duction range need not be large); (c) stereopsis must be present.

5. *Convergence.* Full range with relaxation.

6. *Binocular visual acuity.* For near (bar-reading). For distance (test types). The binocular visual acuity should be equal to the visual acuity in the weaker eye.

Some of my patients, of course, are too young for these tests to be undertaken, but where tests have been carried out it has been found that full binocular function has been restored in 75 percent. In the remaining 25 percent, alternating suppression had set in, usually associated with manifest squints either horizontal or vertical or both. Where the deviation was so marked as to be noticeable, it was corrected by means of cosmetic muscle surgery. Such operations were necessary on six patients. Convergence deficiency caused some difficulty in another six cases; this yielded to orthoptic exercises. Diplopia could occasionally be elicited in some of these patients but none of them complained of diplopia.

C. PSYCHOLOGIC BENEFIT

Striking improvement in the morale and psychologic well-being of these patients has been observed, especially in the group of young adults with traumatic cataract or

traumatic aphakia. This point is best brought out by some typical case histories.

Case histories

CASE 1

A 20-year-old youth was in the Royal Marine Commandos and received a perforating wound of the right eye during exercises. He was invalided out of the Army and given a small pension for the loss of use of this eye. He was very much an open-air type and he had set his heart on a career of this sort. He became very depressed and would not see any of his old friends and made no attempt to get fresh employment. His family were very worried about him and finally his twin brother took the initiative in sending him to me.

He had a healed scar just below the center of the right cornea to which a considerable strand of lens capsule was adherent.

At the first operation this anterior synechia was divided and the strand of capsule was removed, and a peripheral iridectomy was performed.

At the second operation two months later, a 13.5-mm. anterior chamber implant was inserted with the result that he can now see 20/30 unaided and 20/15 with a small minus cylinder. He has full binocular single vision and his mental state has improved out of all recognition. He is looking forward to a career in one of the overseas colonial police forces.

CASE 2

At the age of 14 years, a boy received a severe contusion injury to the right eye from an air gun pellet. He was in the hospital for many weeks and the history suggests that he had a large hyphema with a secondary rise in intraocular pressure. The sight of this eye was reduced to perception of light and a divergent squint developed.

At the age of 35 years, he married a woman somewhat older than himself and, although they were very fond of each other, the sexual side of their married life was a disappointment to both because of the husband's diminished potency. His wife felt that this was due to his brooding over his eye and because ever since the injury he had had to put up with a great deal of unkind teasing, first from his schoolmates, and later on during his army career and at work. She took the initiative in arranging for her husband to consult me. He was 38 years of age when I first saw him.

Owing to the period of secondary glaucoma following the original injury, the optic disc was deeply cupped and atrophic and the field was small and the corrected vision was only 20/100. The intraocular pressure was within normal limits. However, they were so anxious that everything possible should be done that I agreed to try implant surgery.

A peripheral iridectomy was performed and a 12.5 mm. anterior chamber implant inserted. At a later operation the divergent squint was reduced to about -5.0 degrees by muscle surgery. He can now see the expected 20/100 with this eye.

Again the psychologic benefit has been considerable. He has got himself a better job than he had had previously, and I understand that the physical side of their marriage is now satisfactory to both parties. This case shows that considerable psychologic improvement can be expected even when the amount of vision which can be restored is limited by ocular damage in addition to the aphakia.

CASE 3

Following a blow from a piece of wood a 50-year-old woman developed a cataract in her left eye. This was extracted intracapsularly at the age of 60 years. She was a rather nervous patient and never succeeded in overcoming the visual confusion between her normal and her aphakic eyes. She tried numerous pairs of glasses, some designed to give her the use of the aphakic eye while occluding the good one and vice versa.

After some years of this she made an attempt to commit suicide by putting her head in the gas oven. Her daughter turned off the taps just in time, and she was subsequently admitted to a mental hospital as a certified patient with a diagnosis of acute depression.

When I saw her first at this mental hospital, she explained that if only her two eyes could be made to work together once more she would be much better in herself and would not make any further attempts on her life. Her self-diagnosis was supported by psychiatric opinion and she was, therefore, subjected to anterior chamber implant surgery.

The visual result was good, with an acuity of 20/20 and full binocular single vision. Shortly after the operation she was released from the mental hospital and is now apparently leading a normal domestic life.

CASE 4

A Polish boy arrived in the United Kingdom in 1939 as a year-old refugee. At the age of 12 years he was hit in the right eye by a piece of wood, which produced traumatic aphakia. Over the years, he developed a well-marked divergent squint which was later considerably reduced by appropriate surgery. He became very depressed about his near unocular condition, and could not settle down in this country.

At the age of 20 years, he applied to emigrate to Canada, but first, he obtained my opinion as to the possibility of restoring useful sight to this eye with an anterior chamber implant. I considered that this was possible but at that moment he was told that he had been accepted by the Canadian Emigration Authorities and could leave in two months time. I told him that it would not be possible to do this operation and see him through the convalescent period within this period, and that he had to choose between staying in this country for a year or so and having this operation done, or forgetting about it and emigrating to Canada.

He decided that his eye was more important than emigration, and implant surgery has now been carried out. He sees 20/20 and is very pleased. He has now got a better job in this country and is no longer so keen on emigrating.

CASE 5

Two nurses were listening to the 9-o'clock news in the sitting room of the nurses home attached to a South Coast Hospital in 1944, when one of the last shells fired by the Germans across the Channel scored a direct hit. One nurse was killed outright and the other received a perforating wound of the left eye. The iris prolapse was abscised and the wound healed. A traumatic cataract developed over the next year or so and eventually she was given a pension of \$2.00 a week by way of compensation. She subsequently married, gave up nursing and had two children but she found life as a one-eyed person rather trying, and her children did not hesitate to tease her, sometimes unkindly, about her disability.

When first seen 13 years later, at the age of 44 years, she had an inferior iris coloboma with a traumatic cataract. The cataract was extracted intracapsularly with some difficulty because the lens capsule had become adherent to the limbal scar below. Three months later, anterior chamber implant surgery was carried out, and the patient now sees 20/20 with a small correction, and has full binocular single vision.

In this case the patient was always psychologically well adjusted and no great change in her morale is yet noticeable; possibly her long contact with the medical profession has made her view the achievements of surgery with a certain scepticism, and perhaps she wonders if this happy result will last.

Pathologic considerations

None of the patients operated upon have lost an eye and so no material has become available in this way for pathologic examination. However, one patient became mentally disturbed and committed suicide by cutting his throat six weeks after insertion of an anterior chamber implant. I obtained the eye and took it to Prof. Norman Ashton at the Institute of Ophthalmology. It has been intensively examined and we have written a report which is about to be published in the *British Journal of Ophthalmology*. I cannot really anticipate the publication of this report but I can say that there were no findings to discourage the surgeon from inserting anterior chamber implants of this nature into suitable cases.

VI. WHAT IMPACT, IF ANY, DOES THIS
WORK HAVE UPON THE MORE GENERAL
PROBLEMS ENCOUNTERED IN
OPHTHALMOLOGY?

Now, of course, this is a most difficult question to answer. I have only been an operating eye surgeon for about 11 years, during which time I have performed about 2,000 cataract extractions and have also been responsible for about another 500 performed by assistants who come to me for training. I am fully aware that there are many doctors whose experience is much greater than this both in terms of years and of surgery. Therefore, although the possibilities of this technique are very evident, I will resist the temptation to make any sweeping prophecies about the future and will content myself with describing how this technique has affected the way in which I handle the cases presented to me in practice.

a. *Congenital cataracts.* If the child is born with one normal eye, the other one containing a well-marked congenital cataract, I am prepared to operate on the cataract (assuming that the eye is healthy in other respects) as soon as the child is fit enough to stand up to repeated general anesthetics. If the cataract surgery is successful, I will then insert an anterior chamber implant and will occlude the good eye as soon as possible after this to overcome the amblyopia. If the child has bilateral cataract much worse in one eye than the other, I am prepared to carry out this procedure on the worse of the two eyes leaving the other eye untouched.

b. *Traumatic cataract in young children.* It is not possible to fit very young children with contact lenses; therefore, successful treatment of the cataract should be followed as soon as possible with the insertion of an anterior chamber implant and occlusion of the undamaged eye, as for a case of congenital unocular cataract. These cases are of the utmost clinical urgency because amblyopia will occur within a few months of the injury; the younger the child the denser

and the more incurable the amblyopia will be.

c. *Traumatic cataract in older children and young adults.* For these it is sometimes possible to get a satisfactory result with contact lenses but for those where contact lenses are not tolerated or are not wanted or are discarded after a few months trial, the anterior chamber implant should be used.

Occlusion of the good eye is not necessary in these cases because over the age of 10 years, amblyopia ex anopsia will not occur, therefore traumatic aphakia in these older patients can be corrected after an interval of many years.

The record in this respect is held by a man who was hit in the eye by a whip at the age of 10 years. This produced a subluxation of the lens which slowly developed a cataract. At the age of 64 years, I removed this cataract intracapsularly and three months later an anterior chamber implant was inserted. Three years later he has 20/30 vision and full binocular single vision, that is, binocularity was restored to him after an interval of 54 years. Evidently binocular function, when well developed in a patient, is a very sturdy and resilient faculty to survive so long a period of disuse.

d. *Cataract associated with heterochromic cyclitis.* Sooner or later these cataracts must be extracted because of the danger of glaucoma if they are left alone. Contact lenses are not well tolerated in this condition because of the inflammatory element which is present. I have found anterior chamber implants surprisingly satisfactory in these cases.

e. *Unocular senile or presenile cataracts in the 20 to 50-years age group.* Prior to the development of the anterior chamber implant technique, I should have been in no hurry to extract such a cataract but now I am prepared to do so once the vision falls below 20/200. I have found it surprisingly easy to perform intracapsular surgery on these patients and have not, so far, had to use enzymatic zonulolysis to achieve this. These patients do very well with anterior

chamber implants and are very grateful.

f. Unioocular senile cataract in the 50-years and over age group. We are all familiar with the type of patient who submits to extraction of a unioocular senile cataract and cannot be made to understand why cataract glasses cannot be prescribed in the presence of a normal other eye. Elderly patients in my experience are rarely interested in using a contact lens even though these can be provided at no cost to the patient under the National Health Service in my country.

It is very useful to be able to offer such patients a small additional operation for the introduction of an anterior chamber implant. If they decline, well never mind, the offer has been made. If they accept, the surgeon can more or less guarantee a reasonably satisfactory result.

Some of you may be wondering what happens if they get a cataract in the second eye. That has happened in two of my earliest patients. The second cataracts were extracted intracapsularly with a good visual result and I then said to the patients "What do you want me to do? Either I can take the implant out of the first eye or I can put another one in your second eye." They both insisted on having an implant put in the second eye and I, therefore, have these two

cases of binocular aphakia treated with anterior chamber implants.

Only the passage of many years will confirm or modify these practices but, in the meantime, the union which has been established between the use of anterior chamber acrylic implants, the patients, and this surgeon is a very happy one.

9 Drake Road.

ACKNOWLEDGMENTS

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OCHRONOSIS OCULI IN ALKAPTONURIA*

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The purpose of this paper is to record apparently for the first time the histologic findings on an eyeball from a patient whose ochronosis resulted from the congenital type of alkaptonuria. A search of the literature reveals only two histologic studies on ocular tissue, both^{1,2} on excised material. The case reported by Skinsnes³ is worthy of note, since it represented two tragic errors, one of diagnosis and one of commission. The patient's only eye was enucleated because of a mistaken diagnosis of malignant melanoma. The eye, fixed in formalin, was sent to a pathologic laboratory where merely a gross examination was made. The sclera was found to be darkly pigmented, but no neoplastic growth or other abnormality was noted. The discoloration was thought to be due to improper fixation or to fixation artefact, and the specimen discarded. One year later he died, and autopsy showed generalized ochronosis, with striking pigmentation of all cartilages examined.

Hereditary ochronosis may be defined as an inbred disorder of phenylalanine and tyrosine intermediary metabolism, in which the initial expression is usually the spontaneous urinary excretion of homogentisic acid. Ochronosis and alkaptonuria were at one time considered to be synonymous terms, but now it is generally agreed that the alkaptonuria or urinary excretion of homogentisic acid is only one symptom of ochronosis.

The disease is relatively infrequent, manifesting itself in early life and shows a familial pattern often associated with consanguinity. Genetically, ochronosis and albinism are similar, since both are Mendelian recessive traits. This similarity also extends to the conversion of tyrosine into pigment, for in

albinism this transition mechanism is entirely lacking, while in ochronosis the mechanism for breaking down tyrosine further than homogentisic acid is at fault. Homogentisic acid is a normal intermediary compound in tyrosine metabolism, and it is accepted that the excretion of homogentisic acid in alkaptonuria is due to a defect in the enzyme catalyzing the oxidation of homogentisic acid, homogentisic acid oxidase.

LaDu and co-workers⁴ utilizing liver biopsy tissue obtained from the presently recorded case were not able to detect any homogentisic acid oxidase activity, apparently due to a failure to synthesize the active enzyme, rather than to the presence of an inhibitor or to the absence of any known co-factor. Thus, this disorder is another addition to those metabolic derangements known to be due to a defect in a single enzyme system, such as glycogen storage disease, galactosemia, and phenylketonuria.

There is also experimental evidence⁵ indicating that enzymes are under gene control and that single genes may control biochemical reactions through the mediation of specific enzymes. Thus inherited gene alterations or defects in genes may lead to loss of specific enzymes.

Boedeker⁶ (1859) found in the urine of a diabetic a second reducing substance, which turned brown on the addition of an alkali and which he termed alkapton. This reducing substance was later identified as a homologue of gentisic acid, and thus was called homogentisic acid. It was noted that urine containing this matter was of normal color when first voided, but after contact with air turned brown or black, and that linen or woolen articles moistened with the urine took these stains.

Virchow⁷ observed on post-mortem examination a discoloration of cartilage due to pale yellow or "ochre" pigment granules,

* From the Laboratory of Ophthalmic Pathology, Washington Hospital Center. Read at the meeting of the Wilmer Residents Association, Baltimore, March, 1959.

and thus the name "ochronosis" was applied.

In 1902, Albrecht⁸ suggested that ochronosis was caused by alkaptonuria, but Osler⁹ (1904) was the first to describe the clinical features of the disease and make the diagnosis during life, pointing out the pigmentation of the eyes, nose, ears, skin and nails.

The earliest clinical recognition of this disorder may be due to the darkened cartilages of the ear or of the nose, or to the brown pigment spots in the sclera near the insertion of the rectus tendons. Since this is an inherited condition, the defective oxidation of homogentisic acid and its urinary excretion is present from birth, but during the early years there are no harmful effects. Later, however, a percentage of patients develop secondary changes due to the gradual deposition of the homogentisic acid in certain tissues of the body as a peculiar pigment. The disorder is not a harmless curiosity, for a deforming arthritis and spondylitis, severe arteriosclerotic changes in the heart with pigmentation of the valves, the aorta and coronary arteries, and ochronotic nephrosis may appear and progress.

The first comprehensive ophthalmologic publication, including the first slitlamp description, was by von Sallmann.¹⁰ He considered the symmetric arrangement of pigment granules in the corneal periphery and the scleral pigmentation to be of diagnostic significance.

Smith¹¹ (1942) published the best review of this subject in the ophthalmologic literature, and contributed four case reports. At this time he was able to state that the total number of cases recorded, including his own, was 82. As stated in the opening of this presentation, there have been only two histologic reports on excised ocular tissue.

Seitz¹ (1954) biopsied the corneconjunctival margin of an eye and stained the sections with hematoxylin-eosin and with other special stains. He found that in the subconjunctival tissue there were areas in which the elastic fibers were swollen and fragmented, and adjoining were plump yellowish-

brown bodies of variable density. These masses varied considerably in shape and contour and frequently multinucleated foreign-body giant cells were found adjacent to them. In the tiny corneal fragment he found round, yellowish depositions, sharply defined and without a surrounding cellular reaction.

Rodenhäuser² reported the other biopsy material in 1957. He details the clinical and laboratory findings in a 61-year-old man, in whom he excised a segment of bulbar conjunctiva from the temporal side. The sections were stained with hematoxylin-eosin, brilliant cresyl-violet and orcein-hematoxylin-picrofuchsin. He found that beneath the epithelium, the connective tissue fibers were partly fragmented and homogeneous, adjacent to numerous lumps of varying size and without definite structure. He felt that in their appearance and staining reactions these lumps resembled the hyaline masses of a pinguecula, and regarded the disturbance caused by homogentisic acid as a premature senile degeneration of connective tissue.

The case presented here has been studied clinically at the National Institute of Health and published by Bunim¹² and co-workers in 1957.

CASE REPORT

The patient was a 56-year-white man who had been diagnosed as having alkaptonuria in 1949. In infancy his parents noticed that his diapers took on a brownish-black color soon after they were soiled with urine. His urine continued to turn dark upon exposure to air. In 1946, an erroneous diagnosis of diabetes mellitus was made because of the presence of a urinary reducing substance. Since this could not be eliminated by rigid dietary restriction, further investigations established the correct diagnosis. He had progressive symptoms of joint disease dating back to 1934, with a gradual loss of spinal mobility and stiffness of his knees. For about 10 years there has been a gradual deposition of brownish-black pigment in the sclera of each eye, both nasal and lateral to the limbus. There has also been a progressive grayish discoloration of the tip of the nose and both ears, chiefly the conchae. In 1956, he was thoroughly studied at the National Institute of Arthritis and Metabolic Diseases, and the diagnosis of alkaptonuria, ochronosis and arthritis verified.¹³ In February, 1957, an esophageal hiatus hernia was repaired, at which time a liver biopsy had

been performed for enzyme studies.⁴ He was admitted into the Washington Hospital Center on June 18, 1958, because of mental depression and died two days later.

An autopsy was performed and showed deposition of finely granular brown pigment in the tracheal cartilages in a narrow band, diffusely in the costochondral junction, and throughout the substance of the intervertebral disc.

The left eye was removed for pathologic examination.

PATHOLOGIC EXAMINATION OF EYE

GROSS

The specimen consists of a firm formalin-fixed eye measuring 25 by 25 by 24.5 mm. There are two brown spots on the sclera, 2.0 to 3.0 mm. behind the limbus on the nasal and temporal sides, corresponding to the 9- and 3-o'clock positions. The largest, which measures 3.0 mm. in diameter, is situated on the lateral side of the globe between the limbus and lateral rectus. Part of the lesion has a granular appearance. There are numerous brown punctate spots at the corneoscleral margin between the 3- and 4-o'clock positions. The posterior portion of the sclera on the temporal side has a brownish tint. Transillumination is very good except in the area of scleral discoloration where a faint shadow is seen. The eye is opened in the

horizontal plane. An opaque stringy material is present in the vitreous. There is a retinal fold in the macular region. There are no intraocular lesions.

MICROSCOPIC

Examination of the celloidin-embedded tissue shows the corneal architecture to be normal, except that near the temporal limbus there are several subepithelial structureless golden-colored bodies (fig. 1) in the stroma separating the lamellae. There are no cellular reactions in their environs.

The anterior chamber is deep and the angles are widely open. The iris is normal. The lens shows no abnormalities. The posterior portion of the globe is normal.

There is pigmentation of the anterior sclera, both nasally and temporally, in the outer layers overlying the anterior portion of the pars plana. This is most marked on the temporal side. The pigmentation is diffuse, and of a golden color in contrast to the black of the pigment epithelium of the retina and iris. The connective tissue bundles of the sclera are swollen in this area, and are distorted by pigmented clumps (fig. 2) of translucent, structureless substance ranging in size from granules to coalescent masses.

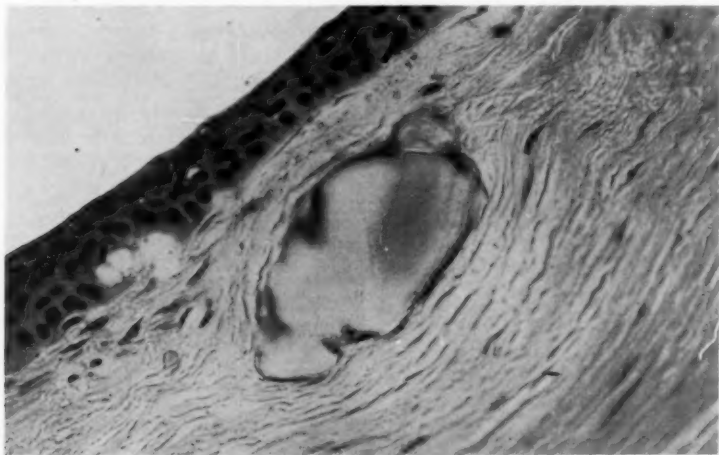


Fig. 1 (Rones). $\times 350$. Subepithelial deposit of golden-colored material in corneal stroma. No surrounding tissue reaction.



Fig. 2 (Rones). $\times 100$. Deposits in sclera and episclera. (Hematoxylin-eosin.)

There is no cellular reaction in this area.

In the neighboring episclera (fig. 2) there are convoluted masses of this golden material which in some sections appear to be in flat platelike shapes. There is a sparse infiltration of large mononuclear cells in this area, and the overlying epithelium is intact.

The hematoxylin-eosin stain was used as the routine technique on these sections. In

an attempt to distinguish the ochronotic pigment from melanin, a battery of staining techniques was employed. There were no differences noted in the preparations which were bleached, stained for melanin, iron, fats, acid and neutral mucopolysaccharides, calcium, phosphate and connective tissues.

The use of special stains did, however, offer some suggestive evidence of the nature

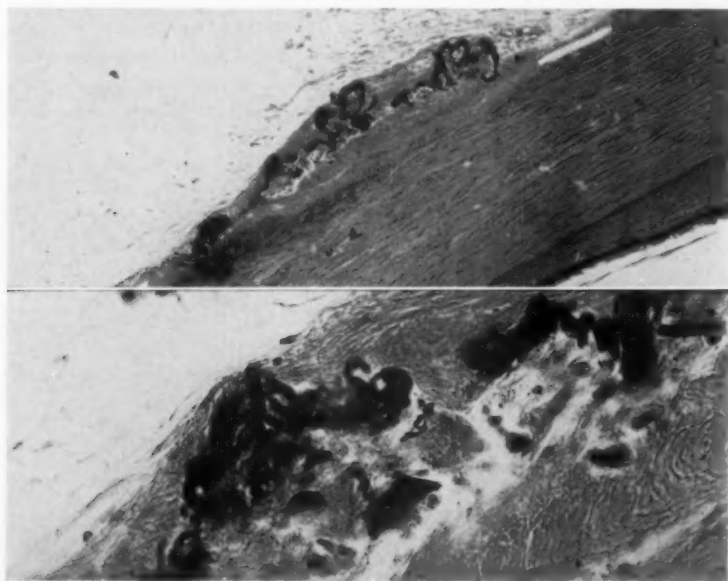


Fig. 3 (Rones). Degenerated elastica in episclera. (Weil myelin stain. [top] $\times 50$; [bottom] $\times 300$.)

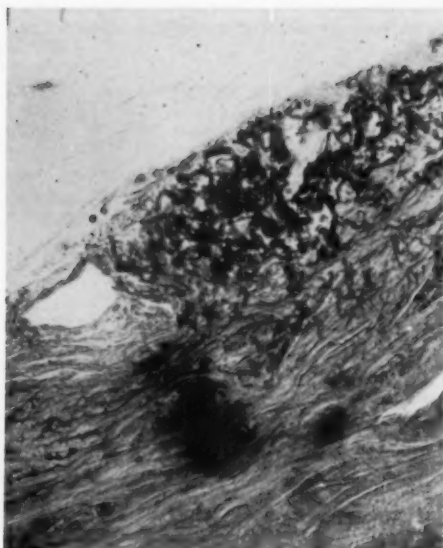


Fig. 4 (Rones). $\times 300$. Degenerated elastica and collagen in sclera. (Weil myelin stain.)

of the tissue reaction, if not of the pigment itself. It is apparent from the study of the cornea, sclera and episclera, that it is the deposition of the melaninlike substance in the collagen bundles of the sclera and cornea, and in the elastic tissue of the conjunctiva and episclera that produces the patterns described. The most rewarding of these stains



Fig. 6 (Rones). $\times 300$. Laminations in episcleral masses of degenerated elastica. (Weil myelin stain.)

are the Weil myelin sheath stain (figs. 3 and 4) and the Verhoeff elastic tissue stain (fig. 5). With both of these stains, the pigment takes a blackish color. In the subconjunctival tissue the elastic tissue fibrils can be traced from their normal wavy fibrils through stages of swelling, fragmentation and mass formation.

In the sclera these masses show the same relationship to the bundles of collagen fibers. It can be seen that these masses are not solid but show laminations (fig. 6) as of age and accretion, and that their surface is not smooth

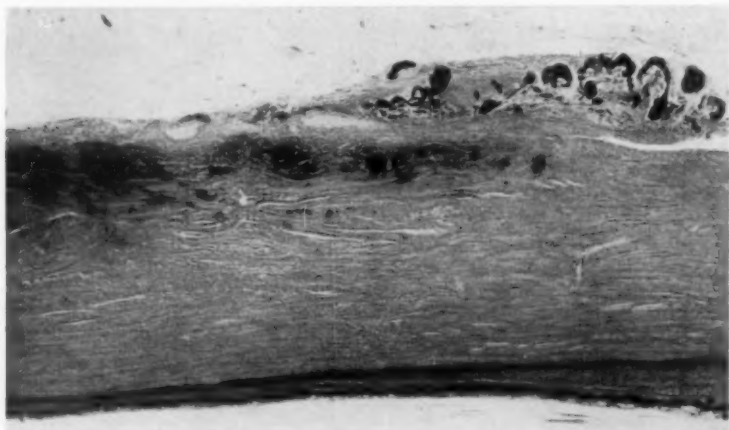


Fig. 5 (Rones). $\times 70$. Degenerated elastica and collagen. (Verhoeff elastic tissue stain.)

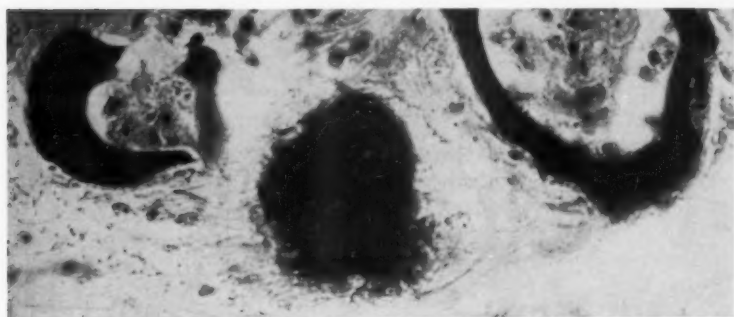


Fig. 7 (Rones). $\times 485$. Irregular "furry" surface of degenerated elastica. (Verhoeff elastic tissue stain.)

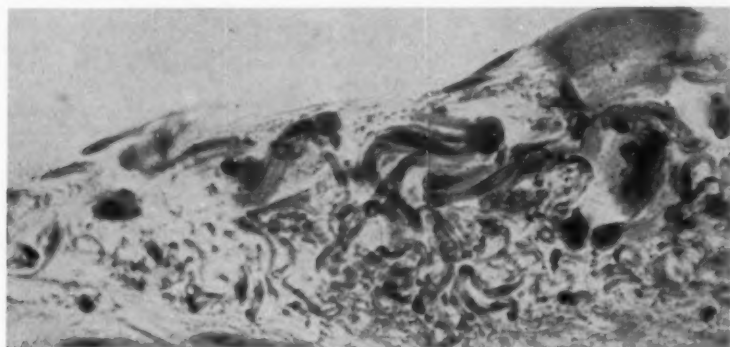


Fig. 8 (Rones). $\times 575$. Degenerated elastica and surrounding mast cells. (PAS stain.)

but presents a "furry" appearance (fig. 7). With the PAS stain (fig. 8) it is evident that the cellular reaction around the degenerated elastic tissue fibers is of the mast cell variety, and the cells are PAS positive. Cresyl violet also stained the pigment almost black, but was not as clearcut as the above two stains.

DISCUSSION

These results were consistent with the observations reported by Cooper and Moran¹³ who utilized electron microscopy and special stains to study ochronotic pigment in various locations in comparison with melanin of normal white skin and melanin of a heavily pigmented nevus. Their chemical studies included extraction and isolation of the ochronotic pigment from cartilage, liver and kidney. They could detect no differences be-

tween ochronotic pigment and melanin, and even though they feel that the exact nature and chemical composition of the ochronotic pigment has not been established it is to be accepted as a melanin or melaninlike substance.

The observations in the present case are in agreement with the biopsied material of Seitz¹ as concerns the episcleral tissue. However, no explanation can be offered as to the localization of the pigment deposits in the eye, particularly the predilection for the palpebral aperture.

SUMMARY

The histopathologic study of an eye containing the ochronotic pigment in a patient with alkaptonuria is offered as apparently the first presentation in the literature. Special stains did not reveal any differences of be-

havior of this pigment from melanin. These stains, however, did suggest that the pigmented material present was the result of degeneration of the elastic tissue fibers and the collagen bundles, apparently the reaction of these tissues to the deposited pigment. The reason for the deposition at the particular sites in the eyes cannot be determined,

nor does speculation offer any fruitful answers.

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I wish to express my deep appreciation to Dr. Henry W. Edmonds for providing the globe from the autopsy, and for his suggestions on the key articles in the realm of general pathology.

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EFFECTS OF ELECTROLYTE MIXTURES ON CELLS FROM HUMAN IRIS*

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AND

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INTRODUCTION

"Normal" saline is commonly employed in the armamentarium of the ophthalmologist as an irrigating solution during the performance of intraocular surgery. This solution has the advantages of being readily available, low in cost and easily sterilized. Several investigators have noted that this so-called "physiologic" saline is actually damaging when placed in contact with living animal cells. The argument that there is little

gross evidence of direct injury should not prevent efforts to investigate the more subtle

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effects brought about by this solution and the consideration of what part it may play in postoperative complications.

Pomerat and Overman¹ have shown by means of tissue culture techniques that cells from the human nasal mucosa were damaged by saline perfusions. The injurious properties of the solution to epithelial cells cultivated both from the organ of Corti and from the middle ear mucosa of the cat were demonstrated by Shambaugh.² Recent studies have revealed that cells from human conjunctiva were relatively undamaged when perfused with saline, whereas the rabbit corneal epithelium was partially damaged and the endothelium was irreversibly damaged (Harper and Pomerat³).

It is not surprising that sodium and chloride ions alone in solution would be found to be inadequate to maintain normal function in cells which are adapted to a very specialized environment containing a complex variety of organic and inorganic substances. The purpose of this study was to check on the vulnerability of cells from the human iris to saline. The effects of several electrolyte mixtures were compared.

MATERIALS AND METHODS

Cellular alteration in response to controlled modifications of the physicochemical environment has been one of the special interests of this laboratory. Experimental studies have been carried out with the aid of double time-lapse cine camera units, perfusion chambers and the technique of film analysis as described in several publications (Pomerat,⁴ Pomerat, Lefeber and Smith,⁵ Pomerat and Smith,⁶ Pomerat and Overman,¹ Pomerat, Kent, and Logie⁷).

The tissue employed in this study was human iris obtained at the time of cataract extraction or enucleation. Specimens were obtained from 10 patients which yielded more than 100 explants.

Explants of tissue measuring approximately one mm. square were washed with Gey's balanced salt solution and embedded

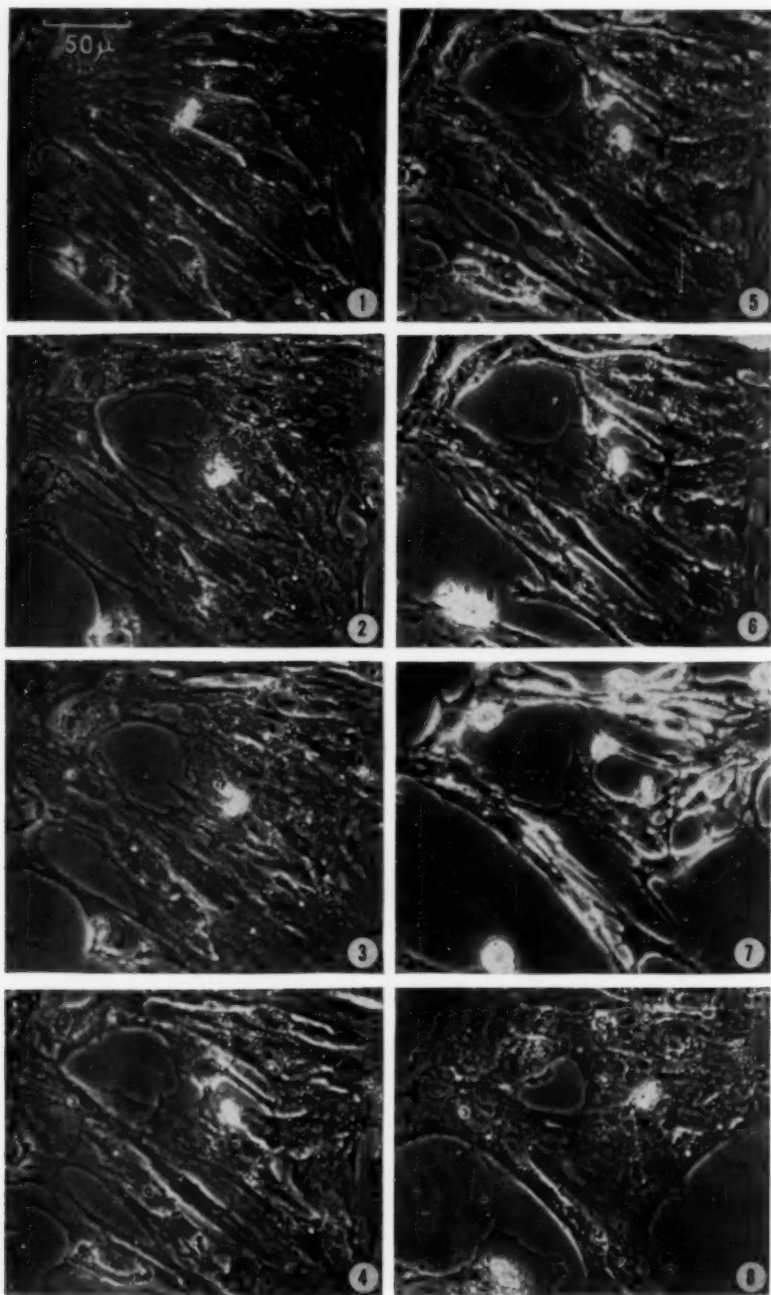
in a clot consisting of equal parts of heparinized cockerel plasma and an extract from eight-day chick embryos, on coverslips measuring 12 by 50 mm. When the clot was firmly set, 2.0 ml. of a fluid nutrient consisting of 50-percent human ascitic fluid of malignant origin, 45-percent Gey's balanced salt solution and five-percent chick embryonic extract, including a final concentration of 1000 units per ml. of penicillin. These conditions have proved useful for the cultivation of various human eye tissues (Pomerat and Littlejohn⁸).

Solutions employed in these experiments were Gey's balanced salt solution, saline and two commercially prepared electrolyte mixtures. A comparison of the constituents of the three test materials is given in Table 1. Solution A was generously supplied by Mead Johnson and Co. and Solution B by Baxter Laboratories, Inc. The pH of the saline was 6.8.

Cell activities in a perfusion chamber were analyzed by means of phase-contrast microscopy. Recordings of the appearance of the cells were made by means of time-lapse photographic techniques. More than 500 feet of 16 mm. records were obtained during the course of this investigation. The optical system employed utilized an eight-mm. dark phase objective without the use of an ocular.

TABLE 1
CONSTITUENTS OF GEY'S BALANCED SALT SOLUTION
AND TWO COMMERCIALY PREPARED
ELECTROLYTE SOLUTIONS

	Gey's BSS ⁹	Solution A Solution B	
		(Gm./1,000 cc.)	
NaCl	8.0	4.9	8.0
KCl	0.38	0.75	0.4
NaHCO ₃	0.25		
CaCl ₂	0.13	0.36	
MgCl ₂ ·6H ₂ O	0.21	0.30	
Na ₂ HPO ₄ ·7H ₂ O			0.0875
Na ₂ HPO ₄ ·12H ₂ O	0.30		
KH ₂ PO ₄	0.025		0.0625
MgSO ₄ ·7H ₂ O			0.2
Glucose	1.0		1.0
NaAcetate		3.9	
NaCitrate		1.7	
pH	7.36	7.16	6.37



Figs. 1-8 (Harper and Pomerat). Selected film frames in a typical perfusion chamber experiment using a 12-day culture of human iris. (See explanation on facing page, bottom)

Acknowledgment is made to Mrs. Walther Hild and Mr. Charles Raiborn for aid in the cultivation of the tissues. The cine records were prepared with the assistance of Mr. George Lefebvre and Mr. Earl Pitsinger.

RESULTS

Explants from the iris showed outgrowth which was characterized by a predominance of spindle cells. These cells were exposed successively for one hour each to the nutrient media, Gey's balanced salt solution, solutions A and B and finally to saline. At the end of this time the nutrient media was reperfused and the cells allowed to remain in contact with this fluid overnight. The protocol of a typical experiment with reference to the figure illustrations of film frames selected at appropriate time intervals appears in Table 2.

The outgrowth in the nutrient medium appeared as spindle cells which were closely packed and presented almost a sheet of tissue. Marked cellular activity was characterized by undulating movements of the cytoplasm and intracellular granule movement.

Perfusion with Gey's balanced salt solution, solution A or solution B produced little change in the activity of the cells. In contrast, the introduction of saline produced a marked effect within five minutes. The cells were individualized as a result of the retraction of the cell processes. Intracellular granule movement and the undulations of the cell membranes were arrested. With the return of the nutrient media the elements again became aggregated with the resumption of cellular activity and about 90 percent of the

TABLE 2
PERFUSION EXPERIMENT ON HUMAN IRIS

Plate I Figure	Solution Perfused	Time in So- lution (min.)
1	Nutrient media	58
2	Fresh nutrient media	58
3	Gey's BSS	58
4	Solution B	58
5	Solution A	58
6	Saline	5
7	Saline	58
8	Nutrient media	58

Total time of experiment was seven hours.

cells apparently recovered from the damaging effects of the saline.

DISCUSSION

The two commercial electrolyte preparations which were evaluated compared favorably with Gey's balanced salt solution, whereas saline perfusion resulted in alterations in the morphologic appearance and activity of cells from the human iris. A marked vulnerability of the corneal endothelium, in contrast to the greater resistance of the epithelium, to damage by the perfusion of normal saline either in vitro or into the anterior chamber of the intact animal has been demonstrated (Harper and Pomerat³). Saline is apparently nondamaging when used as an irrigating solution for the external part of the eye but is not entirely innocuous for bathing the more susceptible structures within the anterior chamber. When performing intraocular surgery it would therefore seem to be reasonable to use an irrigating solution which has been shown to be nondamaging to the cells obtained from the

Fig. 1.* Nutrient media in which the cells had been living.

Fig. 2. After one hour in fresh nutrient media.

Fig. 3. After one hour in Gey's balanced salt solution.

Fig. 4. After one hour in Solution B.

Fig. 5. After one hour in Solution A.

Fig. 6. Five minutes after the addition of saline. The cells show some retraction of their cell membranes.

Fig. 7. Further shrinkage of cytoplasmic processes and individualization of the elements was noted after one hour in saline.

Fig. 8. One hour after the addition of nutrient fluid. Note the re-expansion of cell membranes.

* The scale of magnification for all figures is shown in the upper left area of Figure 1.

delicate tissues being operated upon. The availability of a commercially prepared electrolyte solution for this purpose as well as for washing living cells should prove convenient in many laboratories where cytologic problems are studied.

SUMMARY

The effects of several electrolyte mixtures were observed on cells cultured from the human iris with the use of perfusion chamber technique and phase contrast, time-lapse cinematography. Gey's balanced salt solution and two commercially prepared electrolyte mixtures showed no deleterious effects on the

cells. The perfusion of saline produced definite changes in the appearance and activity of the cells within five minutes. There was retraction of the cytoplasm and cessation of cellular movements. When the nutrient media was re-perfused and allowed to remain in contact with the cells for one hour, about 90 percent of the cells appeared to recover from the damaging effects of the saline.

The advisability of employing commercially available physiologic solutions for washing delicate tissues is suggested.

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ANGIOID STREAKS AND SICKLE-CELL DISEASE*

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In a recent study on ocular manifestations of sickle-cell disease, 69 patients were examined. Of these cases, five patients were found to have angioid streaks in addition to various degrees of sickle-cell retinopathy.

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This relatively high incidence of angioid streaks suggests a possible relationship with sickle-cell disease. The statement by Goodman, von Sallmann, and Holland, in a footnote of their article, that two cases of angioid streaks associated with sickle-cell anemia had been referred to them for examination adds additional weight to such a supposition.

Before attempting to establish a correlation between the two conditions, a review of the clinical and pathologic pictures as well as the theories of etiology relating to both

angioid streaks and sickle-cell disease seems pertinent.

Angioid streaks have been found in several pathologic conditions but are most commonly associated with pseudoxanthoma elasticum. In the five cases described here, only one case was found to have pseudoxanthoma elasticum.

ANGIOID STREAKS

HISTORICAL REVIEW

The clinical picture of angioid streaks was first described by Doyne (1889), who attributed these findings to ruptures in the pigment layer of the retina. Shortly thereafter, Knapp (1892) reported a case of angioid streaks, and at the same time Plang described the occurrence of pigmented striae of the retina. Forty years after Doyne's first description, Groenblad reported three cases with angioid streaks which presented, in addition to the ocular findings, a peculiar skin disease. A dermatologic examination of these three patients by Strandberg proved pseudoxanthoma elasticum, as described by Darrier in 1896, to be present and this author then concluded that angioid streaks were only a part of the same disease, that is, a degeneration of elastic tissue.

Since then, many theories have been postulated as to the site of the ocular lesion. The pathologic reports on two cases of angioid streaks, published by Böck (1938) and by Hagedoorn (1939), substantiated the theory of Groenblad and Strandberg and in both instances the lesions were found to be due to ruptures in Bruch's membrane, due to degeneration of the elastic fibers in the elastic lamina.

Angioid streaks in connection with Paget's disease were reported by Verhoeff (1928), Rowland (1933) and Terry (1934). Only two cases have been reported which presented the triad of pseudoxanthoma elasticum, Paget's disease, and angioid streaks as associated findings (Woodcock, 1952; Shaffer, et. al., 1957).

Other reports by Urbach (1938), Prick

(1938) and Kat and Prick (1940) showed the involvement of elastic fibers in arterial walls as part of a systemic degenerative disease. In actuality, however, Plang (1891) had already reported the clinical observation of a low radial pulse and flattening of the pulse curve in a patient with angioid streaks, which finding he explained as being due to decreased elasticity of the arterial walls. Further reports by deSchweinitz (1896) and Holloway (1927) pointed out the frequent involvement of the systemic vascular system in patients having angioid streaks. Ehlers and Marthinsen carried out the first clinical vascular studies on a patient with angioid streaks and pseudoxanthoma elasticum. Carlborg (1944) gave an extensive review of the literature and reported on 15 cases with angioid streaks combined with peripheral vascular disturbances. Further studies on the peripheral vascular system in patients with pseudoxanthoma elasticum were published by Gunther (1946). Scheie and Freeman (1946) described three cases having the Groenblad-Strandberg syndrome, of which two patients showed peripheral vascular occlusions which were demonstrated in histopathologic studies on one patient. Dixon (1951) reported on a case of pseudoxanthoma elasticum, which had an intracranial aneurysm of the internal carotid artery. Gastro-intestinal hemorrhages in patients with Groenblad-Strandberg syndrome were described by Kaplan and Hartman (1954).

Scheie and Hogan (1957) reported on 10 patients with pseudoxanthoma elasticum and angioid streaks with special reference to general vascular disturbances. These authors showed that, in Groenblad-Strandberg syndrome, most frequently the arterial system of the lower extremities is involved with occasional calcifications and vascular occlusions of varying degree. The pathologic involvement of the arteries of brain, heart, and kidney may be manifested clinically.

Currently, the etiology of angioid streaks is believed to be due to a generalized sys-

temic elastic tissue degeneration in which there is involvement of Bruch's membrane. There are other theories, however, which ascribe the changes to altered collateral circulation with modification of veins, folds in the retina and the pigment layer and fracture of the lamina vitrea.

CLINICAL PICTURE AND DIFFERENTIAL DIAGNOSIS

The diagnosis of angiod streaks is usually not too difficult, if the picture is familiar to the observer. Visual acuity is decreased only if the macular area becomes involved. Otherwise, angiod streaks are symptomless. Since pseudoxanthoma elasticum is part of a generalized degeneration of the elastic tissue, vascular symptoms may be present. Such symptoms depend on the location of the involved vessels and the severity of the pathology.

Funduscopy examination reveals a network of dark-brown, brownish-red or grayish lines or streaks, suggestive of cracks in an old painting. These streaks may be of varying widths and, as a rule, they are located in the posterior part of the eye. They take origin usually in a radiating fashion from a somewhat white or pinkish small ring around the disc and then pursue their course peripheralward. The streaks are often interrupted and irregular and criss-cross each other. Occasionally, the dark streaks show grayish-white borderlines which extend a variable distance. The radiating streaks may be crossed by thin, concentric, dark pigmented lines at varying distances from the disc. The entire fundus appears often slightly hazy and grayish. The retinal vessels always pursue their normal course superficial to the angiod streaks (fig. 1).

In the differential diagnosis, one may think of striate retinitis and traumatic tears of the choroid. In striate retinitis, the streaks are not so sharply borderlined, and also there are usually other signs of an earlier retinal detachment. Such striae have been described by Roune (1910) and Leber

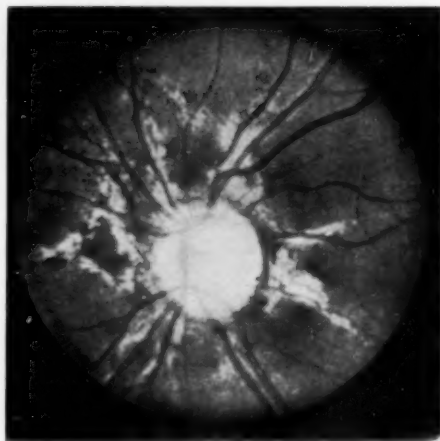


Fig. 1 (Geeraets and Guerry). Funduscopy picture of angiod streaks.

(1916) and are said to be caused by a strand of connective tissue between choroid and retina. Tears in the choroid may be located at any place in the fundus and rarely radiate from the disc. They tend to be more regular in configuration and there is always a history of trauma.

Siegrist (1899) described streaks in arteriosclerosis which are usually darker and more irregular.

A frequent ocular finding associated with the angiod streaks is macular involvement, caused by hemorrhages or transudates which, in advanced cases, appear similar to those seen in Kuhnt-Junius disease.

The visibility of the streaks was explained by Böck as being due to changes in the pigment epithelium overlying ruptures in Bruch's membrane. In case the pigment epithelium is absent, the choriocapillaris may be seen. Due to proliferation of the pigment epithelium over the ruptured membrane, the streaks may vary in color.

According to Hagedoorn, the translucency of Bruch's membrane is abnormal and therefore causes the grayish appearance of the fundus, while in areas of the ruptured membrane, the red reflex of the choroid can be seen directly appearing as red streaks. The occasional clinical appearance of whitish

colored streaks is thought to be due to a secondary membrane closing the ruptures.

PATHOLOGY AND DIFFERENTIAL DIAGNOSIS OF ANGIOID STREAKS

The pathology generally found in eyes of patients with the Groenblad-Strandberg syndrome will be described first. A detailed discussion on this subject was given by Böck (1938), Hagedoorn (1939) and Verhoeff (1948).

It should be mentioned in passing that ocular findings occur most frequently in combination with pseudoxanthoma elasticum. They also occur in association with osteitis deformans, retinitis albuminuria, generalized vascular disease, myopia and after eye injury and inflammation.

BRUCH'S MEMBRANE

As already mentioned, the pathology of angioid streaks is usually described as being located in Bruch's membrane. In this respect, it must be remembered that this structure consists of two layers—the basal layer of the pigment cells and the outer or Bruch's layer. One of the most characteristic pathologic findings in the Groenblad-Strandberg syndrome is the basophilic staining of Bruch's layer in many places. Hagedoorn has shown that in areas where the outer layer and the basal layer had been separated by exudates, only Bruch's layer shows intensive basophilic staining. The basal layer, which always remains firmly attached to the pigmented cells, seems to be unimpaired. From this, the author concluded that the basal layer does not take part in the degenerative process, while Bruch's layer does. Furthermore, this basophilic staining of Bruch's layer was only found in those eyes presenting the angioid streaks associated with pseudoxanthoma elasticum. In all cases in which the angioid streaks were of a different etiology, this staining proclivity was not present.

Orcein elastic tissue stain did not stain some areas of Bruch's membrane at all or

only poorly, while in other areas the staining of the elastic tissue appeared normal.

Another interesting feature was reported by the same author, who found that Bruch's layer showed a positive Turnbull blue test. This reaction was thought to be due to iron precipitates in the presence of primary calcium deposits. The author believed that this finding might play a part in the development of angioid streaks.

Recently, electron microscope studies were done by Loria, et. al., in a case of pseudoxanthoma elasticum associated with angioid streaks. These studies purport to show a deposition of foreign material in or on the elastic tissue which is consistent with the findings of mineral depositions, especially calcium salts. Other tissues do not show such changes according to the authors.

Finnerud and Nomland (1937) described calcification of elastic tissue in pseudoxanthoma elasticum. According to these authors, the high calcium content in the areas of degenerative elastic tissue does not bear any fundamental relationship to the pathologic process of this disease but it was thought to be a part of a generalized pathologic process in which elastic tissue, wherever located, is predisposed to calcification.

Lobitz and Osterberg (1950) found that in the tissue with degeneration of elastic fibers in pseudoxanthoma elasticum, a heavy concentration of calcium exists. They recorded the percentage of calcium in the ash weight in one case as being 33.2 percent and in another case, 32.7 percent as compared with 4.6 percent in normal skin.

Shaffer, et. al., indicates that the defect is to be found in the collagen rather than the elastic fibers. Special staining with Mallory's phosphotungstic acid-hematoxylin stain demonstrated that degenerated fibers were increased. Electron microscopic studies by Tunbridge, et. al., showed the collagen fibers to be shorter than they appear normally while there was no increase in true elastic tissue.

In Böck's case, Bruch's membrane was

irregularly thickened, while in Hagedoorn's case the membrane was thickened in the periphery and became thinner in the posterior portion. The ruptures in Bruch's membrane vary in size and show generally rounded or sharp margins. If transudates, hemorrhages or connective tissue proliferation occur between pigment epithelium and Bruch's membrane in the macular area, the clinical picture is similar to that of disciform macular degeneration.

PIGMENT EPITHELIUM

As already mentioned, the pigment epithelium may be separated from Bruch's layer by exudate, hemorrhage or connective tissue proliferation. Although it may show degenerative signs over larger defects in Bruch's membrane or may even be absent in such areas, it is generally not involved in areas where Bruch's membrane is intact.

RETINA

The inner layers of the retina are usually normal, but the rods and cones may be affected. In general, there is minimal reaction in the choroid where the ruptures in Bruch's membrane occur, but occasionally proliferation of glial tissue or cicatricial tissue may extend through the ruptures under Bruch's membrane. Sclerosis of retinal arteries is not a significant feature of the pathology.

CHOROID

Defects in the elastic layer of one of the larger choroidal vessels were described by Böck. Similar defects could be demonstrated by the same author in the ciliary arteries around the optic nerve. Hagedoorn described the choroid as being characterized by prominent arteries with thick vessel walls and a generally pale appearance of the entire choroidal tissue. In contradistinction to arterial changes in arteriosclerosis, fatty infiltration or hyaline degeneration and proliferation of intima cells are not present. In particular, the larger vessels in the posterior region are involved. The elastic fibers in the

vessel wall may completely disappear, but the lamina elastica interna usually remains. The degeneration of the elastic fibers is often compensated for by hypertrophy of the smooth muscles which causes the thickness of the vessel wall and occasionally vessel obliteration. In Hagedoorn's case specifically the ciliary vessels close to the optic nerve showed absence of elastic fibers of the inner part of the vessel wall, thus differing from the changes noted in arteriosclerotic vessels.

CORNEA

The only pathologic finding of note in the cornea may be a subepithelial degeneration of the limbal area but this occurs rather frequently.

BIOCHEMICAL PROPERTIES OF ELASTIC TISSUE

The characteristic substance in yellow elastic fibers is elastin. Of the three types of fibers peculiar to connective tissue, elastin is probably the least understood. This is due mainly to the difficulties of obtaining large quantities of elastin, particularly from human tissue. For this reason, most of the studies have been carried out with mammalian elastic tissue, mainly with cow ligamentum nuchae.

Elastin is an insoluble protein and resembles collagen in composition. According to Bowes and Kenton (1949), it is the only protein in mammalian tissues containing significant quantities of hydroxyproline (2.0 percent). Elastin is not dissolved in the human digestive tract but it may be dissolved by elastase, an enzyme which has been obtained from beef pancreas (Balo and Banga, 1950). Under the action of elastase, no amino acids are liberated. Hall, Reed and Tunbridge (1952) deduced the fact that elastic fibers are built by proelastin units, which are arranged in a linear fashion and stabilized by an interchain matrix consisting of proelastin acid polysaccharide complexes. Electron microscopic studies of elastic tissue showed a compatible picture. The fibers

showed nonstriated fibrils in parallel alignment lying in an amorphous matrix.

The amino-acid content of mammalian elastin according to Felsher is:

AMINO ACID	ELASTIN IN COW LIG. NUCHAE	
	(gm./100 gm. protein)	
Total N	17.1	
Amino N	—	
Glycine	29.9	
Alanine	18.9	
Leucine	8.7	
Isoleucine	4.0	
Valine	17.4	
Phenylalanine	5.0	
Tyrosine	1.61	
Tryptophane	0.01	
Serine	0.82	
Threonine	0.96	
Cystine	0.15	
Methionines	0.03	
Proline	17.0	
Hydroproline	2.0	
Lysine	0.39	
Hydrolysis	—	
Arginine	0.89	
Histidine	0.07	
Aspartic acid	0.63	
Glutamic acid	2.1	
Amide—N	0.04	

SICKLE-CELL DISEASE

The comprehensive literature on the gross clinical manifestations of sickle-cell disease, especially with regard to its ocular manifestations, has recently been reviewed and reported on by Lieb, Geeraets, and Guerry based on observations made in 65 cases. In this monograph, in addition to various theories as to the causes of fundus pathology, the observable funduscopic changes were classified into four grades according to severity, and fundus changes of equal severity were found in both S-S and S-C groups (fig. 2).

Fundus pathology was graded as follows:

Grade I. Increased tortuosity and dilatation of the retinal veins with mild ischemic areas in the outer periphery of the retina.

Grade II. Neovascularization and microaneurysms of the venules in the periphery, as well as circumscribed narrowing of the blood column in peripheral venules, along with ischemic areas.

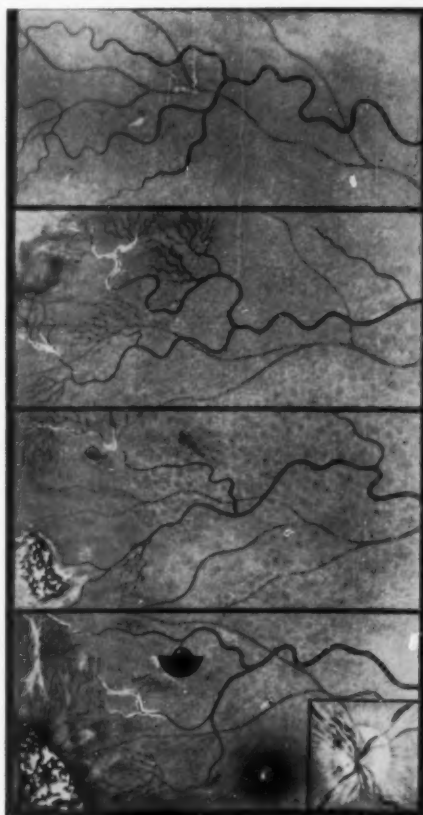


Fig. 2 (Geeraets and Guerry). Grade I to IV sickle-cell retinopathy (classification after Lieb, Geeraets, and Guerry).

Grade III. Retinal hemorrhages and exudates in addition to the changes of Grade II and with small or large areas of chorioretinal atrophy.

Grade IV. Retinitis proliferans, vitreous hemorrhage and occasionally papilledema.

Microscopic pathologic findings such as old and fresh vitreous hemorrhages, sub-, intra-, and preretinal hemorrhages, exudates and extensive new formation of capillaries particularly close to the ora serrata were demonstrated. Some of the more recent theories concerning the general disease as well as its ocular changes may be discussed here.

It is well known that sickle-cell disease is

a hemolytic disorder apparently inherited as a Mendelian dominant. Pauling, Itano, Singer and Wells (1949) demonstrated the characteristic different electrophoretic patterns of sickle-cell and normal hemoglobin. Since this discovery, other different types of hemoglobin have been found to cause similar pathologic manifestations. Today, sickle cell disease is classified into five main groups:

Combination of normal hemoglobin A with sickle-cell hemoglobin S is known as sickle-cell trait. This is usually asymptomatic and is present in approximately eight to 11 percent of the American Negro population.

In two to three percent, the combination of hemoglobin A with hemoglobin C, which is another electrophoretically different type of hemoglobin, is found. A-C patients usually are asymptomatic.

In true sickle-cell anemia or hemoglobin S-S disease, characteristic clinical manifestations are striking and can be observed in the very young. There is considerable shortening of the patient's life span in this group.

Combination of S and C hemoglobin leads to similar changes such as those observed in S-S disease.

Hemoglobin C-C has been reported in only a small number of cases. Patients with hemoglobin C-C show a normocytic hemolytic anemia with many target cells in the peripheral blood.

Characteristic findings in sickle-cell disease are anemia, joint pain, leg ulcers, acute abdominal pain and ocular manifestations such as those already described.

The typical laboratory finding in sickle-cell anemia is the formation of sickled erythrocytes under low oxygen tension. Sickling can be prevented either by addition of oxygen or by removing carbonic anhydrase from the cells. Wintrobe found that lysine and valine are decreased in the globin moiety of the sickle cells but serine is increased and, in addition, there is an increased resistance to hypotonic solutions. The sickling of deoxygenated cells is explained by the bending of

the parallel alignment of the amino acids in the globin moiety, thus causing alteration of the red cell membrane.

Another interesting feature of the disease has to do with the so-called crisis. In this condition, brought about by decreased bone marrow production, there is a rapid fall in hemoglobin, increased leukocytosis and an early diminution in reticulocytes. Clinical signs of crisis are: abdominal pain, fever, shortness of breath and any of the multitudinous symptoms caused by vascular stasis and occlusion.

Ocular involvement in sickle-cell anemia was reported by Cook (1930), who found retinal hemorrhage associated with subarachnoidal hemorrhage. Since then, many publications have dealt with this subject and several theories have been elaborated to explain the cause of neovascularization.

The principal reason for the ocular changes may be explained by the low oxygen tension of the blood. Since S-hemoglobin increases its viscosity if its concentration is raised above 12 gm./100 ml., it is apparent that stasis within the small vessels may occur. This is most pronounced under low oxygen tension. Due to a crystalline or paracrystalline intracellular reaction—caused by the hemoglobin in an anoxic state—the erythrocytes become deformed (Perosa). Ingram explained the sickling to be due to a difference in one amino acid in S hemoglobin compared with normal, which causes a difference of the charge distribution on the surface of the molecule. After splitting the hemoglobin molecule by the action of trypsin, he analysed the fragments by the use of a combination of electrophoresis and chromatography. In this way, the author was able to demonstrate that only one molecule of glutamic acid in the amino acid chain of normal hemoglobin A is replaced by one molecule of valine in hemoglobin S, respectively, one molecule of lysine in hemoglobin C.

Since glutamic acid has a negative electrical charge, the substitution by lysine—

which is electrically positive—produces a greater electrical charge of the molecule than the substitution of valine, which is electrically neutral.

With the stasis in the small venules and clumping of sickled cells, the already existing hypoxemia becomes still more severe and results in the train of events which was so ably expounded by Wise in his extensive reports on this subject.

CASE REPORTS

CASE 1

G. T. (41) 26-year-old man. The patient was hospitalized 18 times since the age of 11 years for clinical manifestations of sickle-cell disease. During this time, he went into crisis 10 times and received numerous blood transfusions. Hemoglobin ranged from 1.4 to 7.0 gm. at times of admission, RBC from 1.7 to 2.2 million and WBC 9800 to 20,300. Prothrombin concentration, 38 percent. Positive sickle-cell preparations with occasional target cells in peripheral smears. Protein (albumin) 4.5, (globulin) 3.8, bilirubin 0.8D and 3.6T-STs negative—normal blood sugar. Hemoglobin electrophoresis showed hemoglobin S-S.

Besides crises, associated symptoms and signs were leg ulcers, mild albuminuria, priapism and occasional visual disturbances.

Fundus examination revealed a star-shaped area with irregular dark pigmented lines, extending to the midperiphery of the retina. The entire retina appeared slightly hazy and anemic. The radiating streaks were bordered by black pigmented lines. Veins and capillaries showed increased tortuosity. Old hemorrhage was present in the macular area and mild neovascularization with few microaneurysms in the upper temporal quadrant. No fresh retinal hemorrhages or retinitis proliferans could be observed. (Grade II-III sickle-cell retinopathy).

Examination of the skin revealed changes typical of pseudoxanthoma elasticum on the left side of the neck. No other signs of this disease were found (fig. 3).

CASE 2

H. C. (48) a 25-year-old woman had been hospitalized previously with sickle-cell crisis. Hemoglobin at the time of admission was 2.2 gm. with an average of 6.6 gm. RBC, 2.5 to 3.0 million; WBC ranged from 14,500 to 18,000. Sickle-cell preparation positive. Hemoglobin electrophoresis showed hemoglobin S-S. Bilirubin 1.3D and 5.0T. STS negative, normal blood sugar. Pulmonary infarction at the age of 23 years. No pseudoxanthoma elasticum skin lesions demonstrated.

Fundus examination showed a small irregular grayish area around the disc and eccentric, dark pigmented or white thin lines at varying distances from the disc, principally in the left eye. Dark



Fig. 3 (Geeraets and Guerry). Pseudoxanthoma elasticum in patient with sickle-cell anemia. Involvement of the elastic tissue in skin folds of the neck.

brownish-red streaks radiated from the disc area outward to the midperiphery, partially bordered by grayish gliomatous tissue. The macular area in both eyes was dark brownish-gray, surrounded by hazy grayish-white retina. The retinal veins were distended and tortuous. Large ischemic areas were seen in the far periphery with new vessel formation and microaneurysms. In O.S., a sharply demarcated whitish area with black, patchy pigment deposits was found, and close to this area, neovascularization protruded into the vitreous. In O.D. at the 7-o'clock position, a small pre- and intra-retinal hemorrhage was found (Grade IV sickle cell retinopathy) (fig. 4)

CASE 3

M. A. (57) 30-year-old woman, hospitalized once for pre-eclampsia and at 29 years of age for leg ulcers. No crisis was previously reported. Hemoglobin ranged from 6.8 to 9 gm., RBC, 2.6 to 3.5 million, WBC, 14,600 to 19,200. Reticulocyte count between 32 and 40 percent. Bilirubin 3.4D and 5.2T. STS negative. Normal blood sugar. Sickle cell preparation positive with frequent target cells in the peripheral blood smear. Hemoglobin electrophoresis showed hemoglobin S and C.

No skin lesions were present.

Fundus examination showed a circumpapillary, ring-shaped grayish-white area from which

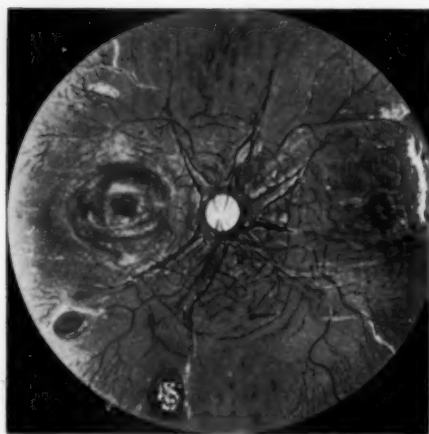


Fig. 4 (Geeraets and Guerry). Fundus drawing (No. 48). Angioid streaks with involvement of the macula. The patient presents in addition a Grade IV sickle-cell retinopathy.

grayish-brown streaks radiated toward the periphery. The streaks showed serrated margins and were connected by thin, irregular, darkly pigmented lines. Close to the disc the streaks showed a width of about twice that of a retinal vein and were more pronounced in the right than in the left eye. Except for peripheral ischemic areas, general tortuosity and mild sheathing of the retinal veins and capillaries (Grade I-II sickle-cell retinopathy), no other ocular findings were present.

CASE 4

L. S. (69) 11-year-old boy previously hospitalized with osteomyelitis (?) of his right hip. Hemoglobin between 6.5 and 8 gm., RBC, 2.5 to 3.1 million, WBC 21,000 to 32,600. Bilirubin 1.1D and 2T. STS negative. Protein (albumin) 2.6 and (globulin) 4.2. Sickle-cell preparation positive. Hemoglobin electrophoresis was not repeated after questionable result, since the patient had already been discharged from the hospital and lived several hundred miles away. No skin lesions were found.

Fundus examination showed a small brownish pigmented ring around the discs which was, in the left eye, incomplete and only present at the temporal side as well as above and below the disc. Small irregular curved streaks, brownish-red in color, redder in certain areas, radiated toward the periphery. A retinal hemorrhage was present in and around the macula in the right eye. The entire retina in both eyes appeared slightly grayish and hazy. Ischemic areas in the temporal periphery with general increased tortuosity of retinal veins, particularly of the small capillaries, were seen in both eyes. In O.S., small sausage-like dilations of several small venules with stasis of the blood column were observed. No neovascularization or

proliferation was found (Grade I-II sickle-cell retinopathy).

CASE 5

J. B. (6). This 26-year-old man with sickle-cell hemoglobin C disease did not present the typical fundus findings of angioid streaks. He presented peculiar brown pigmented lines in the upper temporal quadrant, mainly in the periphery. These lines circumscribed the disc and showed frequent anastomoses. They were crossed by other irregular radiating lines. Although it cannot be stated that these lines were ruptures of Bruch's membrane, they showed a striking similarity to those found in eyes with angioid streaks.

Besides these changes, there were several large peripheral areas of chorioretinal atrophy, neovascularization and deposits of cholesterol crystals as well as sheathing of small tortuous venules (Grade III sickle-cell retinopathy).

HISTOPATHOLOGY

The histopathologic findings in eyes presenting angioid streaks funduscopically have already been described. A comparison of these changes with those occurring as ocular manifestations in sickle-cell disease follows.

Histopathologic studies were done on two eyes (No. 66) which were obtained as autopsy specimens from a 46-year-old Negro patient. Autopsy was performed two hours post mortem. The patient had sickle-cell anemia and presented electrophoretically S-S type hemoglobin. The cause of death was sickle-cell crisis. The eyes had been reported clinically as negative except for scleral icterus but a thorough fundus examination through dilated pupils had not been carried out.

Sections stained with hematoxylin-eosin showed Bruch's membrane to be thicker in the posterior segment of the globe. The characteristic basophilic staining of the membrane as described by Hagedoorn in eyes with angioid streaks could not be demonstrated in our sections. Staining with Verhoeff's elastic stain and Orcein, however, showed large areas in Bruch's membrane to be completely devoid of elastic fibers, particularly in the posterior segment of the globes (Fig. 5-a and b), although occasionally such defects were found in the periphery as well. In a few sections Bruch's

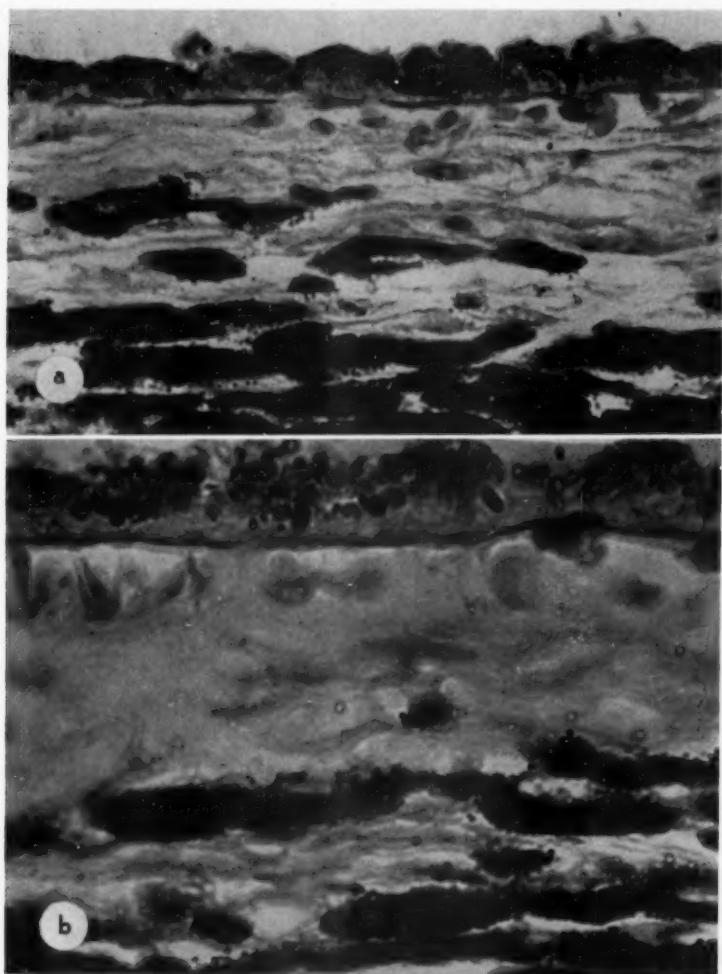


Fig. 5—a and b (Geeraets and Guerry). Defects in Bruch's membrane (Verhoeff's elastic tissue stain, $\times 600$).

layer was separated from the basal layer of the pigmented epithelium with some homogeneous material interspersed between both structures (fig. 6). The pigmented epithelium appeared to be normal in areas of Bruch's membrane where the defects were located (fig. 7). Calcium deposits of Bruch's membrane could not be demonstrated since the specimens had been previously fixated with Bouin's fluid.

Iron staining (Turnbull blue test) showed many small areas with hemosiderin deposits in the choroid but did not stain Bruch's membrane. In some of the sections, a homogeneous markedly thickened eosin staining lesion in the nerve fiber layer of the retina was found (fig. 8). This lesion was close to the disc opposite to the macula and involved the inner plexiform layer, ganglion cell layer and nerve fiber layer. Within this thickened

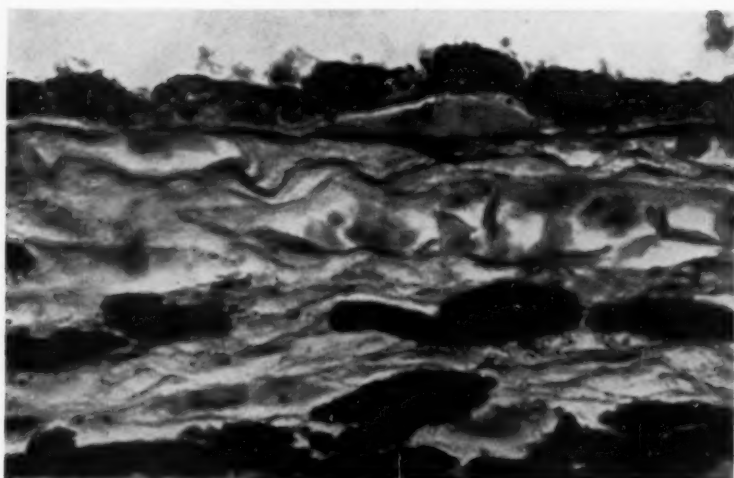


Fig. 6 (Geeraets and Guerry). Separation of Bruch's layer and the basal layer of the pigmented cells by some homogenous material (Verhoeff's elastic tissue stain, $\times 700$).

area, several small capillaries were seen, some of which had been obliterated by hyaline thickening of the capillary wall and others by congested and sickled erythrocytes (fig. 9). Similar eosin stained areas were found in the periphery of some sections with the lesion located in the outer plexiform layer. The retinal vessels did not show

significant changes except for congestion and intravascular sickling (fig. 10). In one area of several sections the nerve fiber layer was thickened to three or four times its normal thickness with many small, new-formed capillaries. A defect in the rods and cones layer was found in another area. (fig. 11).

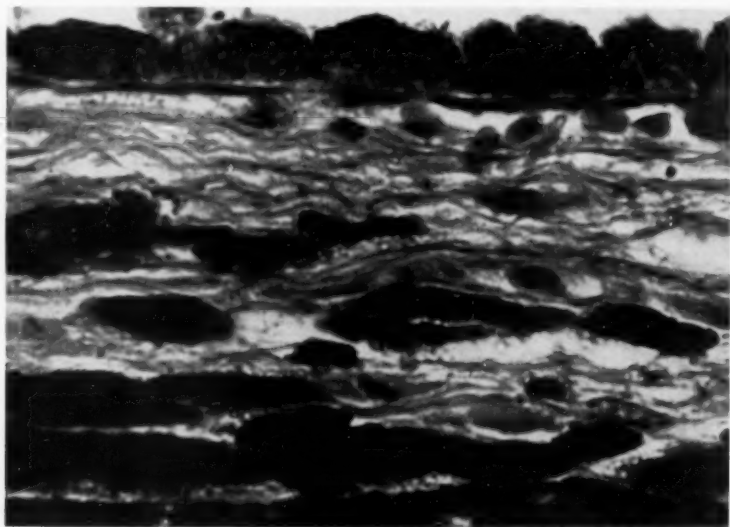


Fig. 7 (Geeraets and Guerry). Normal pigment epithelium overlying small defects in Bruch's membrane (Verhoeff's elastic tissue stain, $\times 700$).

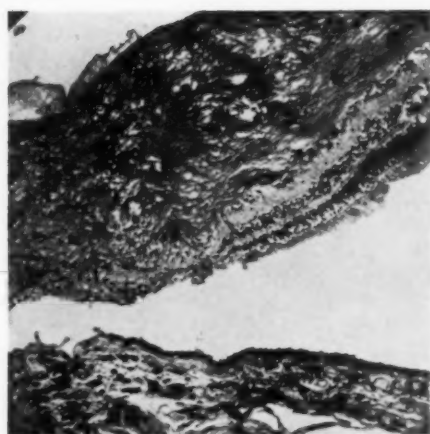


Fig. 8 (Geeraets and Guerry). Homogenous markedly thickened eosin-staining lesion close to the disc (Hematoxylin-eosin, $\times 160$).

Except for some thickening of the walls of the capillaries close to the disc, no other disturbances of the retinal vessels could be seen.

The main pathologic feature in the choroid was congestion of the choroidal veins which were filled with sickled erythrocytes. Since

these changes were found principally in the posterior part, it may very well represent post-mortem changes. The walls of the choroidal arteries were thickened but not as markedly as those described by Hagedoorn in eyes with angiod streaks.

Breaks and irregularities in the lamina interna of one choroidal artery were found in several sections (fig. 12-a and b). These findings were similar to those described by Böck. As already mentioned, numerous small areas with hemosiderin deposits were located throughout the choroid.

Some of the long ciliary vessels showed similar defects in the tunica elastica interna as was seen in one choroidal artery. The elastica was interrupted in several places and completely absent over a large area in another vessel (figs. 13 and 14). In those areas where the elastica was involved, there was an additional formation of connective tissue in the vessel wall.

The central retinal vessels showed only a mild thickening of their walls without an increase of elastic tissue.

Eye No. 63 was from a 19-year-old Negro

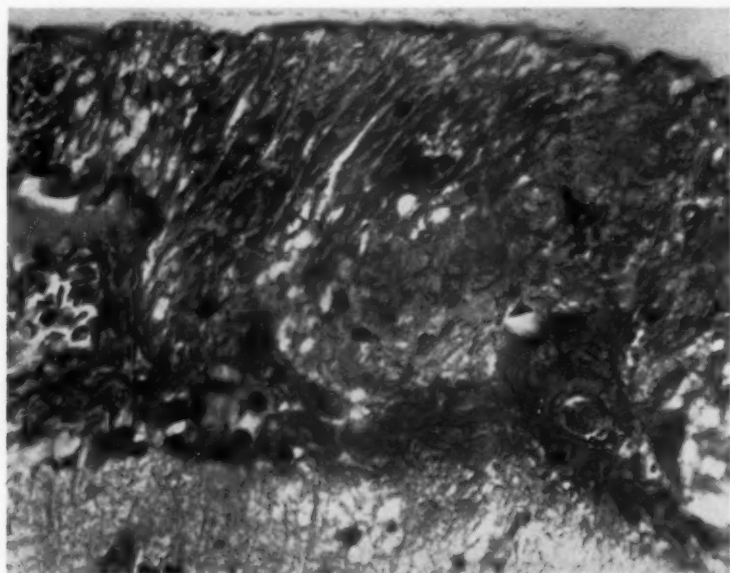


Fig. 9 (Geeraets and Guerry). Enlarged section of Figure 8 demonstrating intravascular sickling and hyaline thickening of the capillary wall (Hematoxylin-eosin, $\times 480$).

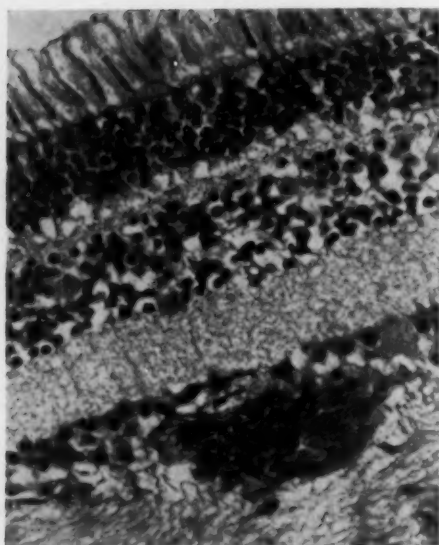


Fig. 10 (Geeraets and Guerry). Retinal vein with intravascular sickling (Hematoxylin-eosin).

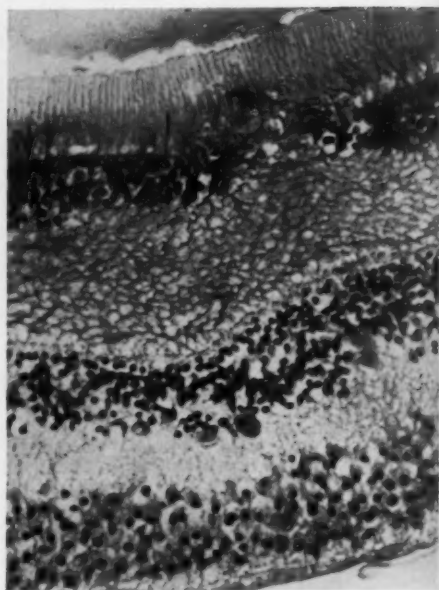


Fig. 11 (Geeraets and Guerry). Small defect in outer nuclear layer (Hematoxylin-eosin, $\times 480$).

who had sickle-cell hemoglobin C disease. Previous ophthalmoscopic fundus examination did not reveal signs of angioid streaks, but did show a Grade IV sickle-cell retinopathy, that is, retinitis proliferans and retinal and vitreous hemorrhages. Similar eye-ground changes, although not as severe as

in the enucleated eye, were found in the other eye. Dermatologic examination showed no evidence of pseudoxanthoma elasticum. The histopathologic findings cannot be regarded as significant for sickle-cell disease,

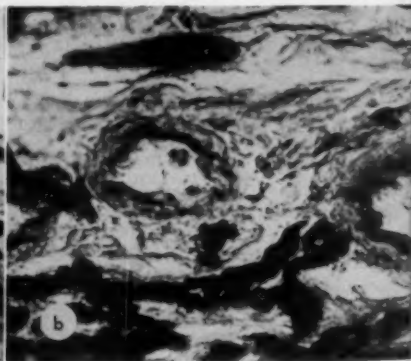
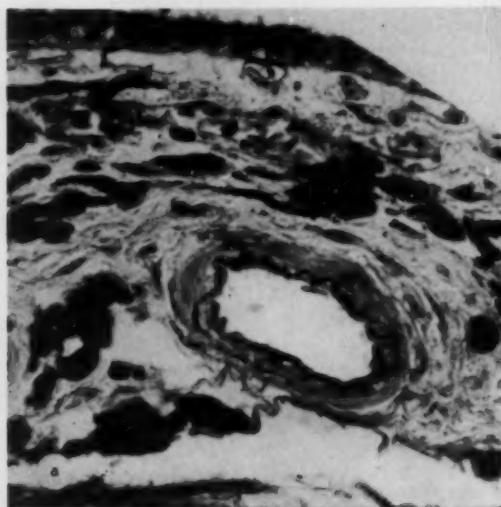


Fig. 12 (Geeraets and Guerry). (a and b) Defect in the lamina elastica interna of a choroidal artery (Verhoeff-van Gieson, $\times 130$).

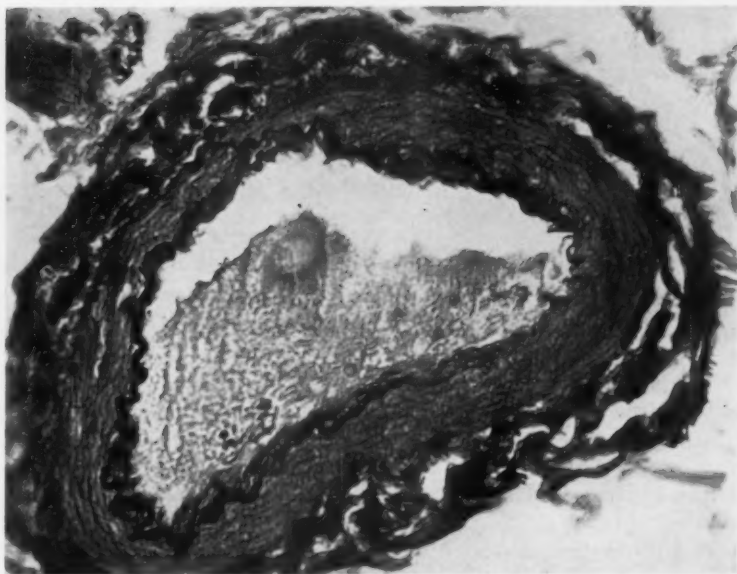


Fig. 13 (Geeraets and Guerry). Defect in the lamina elastica interna of a long ciliary artery (Verhoeff-van Gieson, $\times 325$).

since other intraocular pathology may grossly cause a similar picture. Of particular interest in this eye are the changes which show a striking similarity to those noted in eyes with angioid streaks.

BRUCH'S MEMBRANE

Several areas of the membrane mainly in the posterior segment of the eye were thickened and showed loosening of the structure. More peripherally on either side of the disc, Bruch's membrane was completely absent and the margins in the areas of such defects appeared sharp without curling of the edges. Proliferative fibrinogenous tissue separated Bruch's layer from the basal layer of the pigment epithelium in a few small areas. Furthermore, the tissue proliferation penetrated both Bruch's membrane and the pigment layer and numerous capillaries were to be seen in this invading tissue (fig. 15).

Within this area, segments of Bruch's membrane were still present but in part dislocated. The outer pigment layer of the retina had partly undergone a degenerative

process in the area of the destroyed Bruch's layer. The choriocapillaris had disappeared. Old and fresh subretinal hemorrhages and

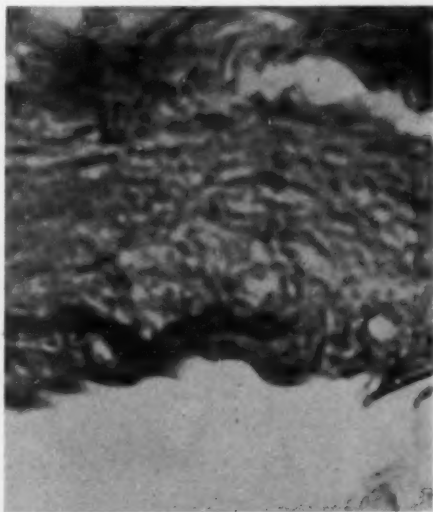


Fig. 14 (Geeraets and Guerry). Enlarged section of the preceding long ciliary artery.

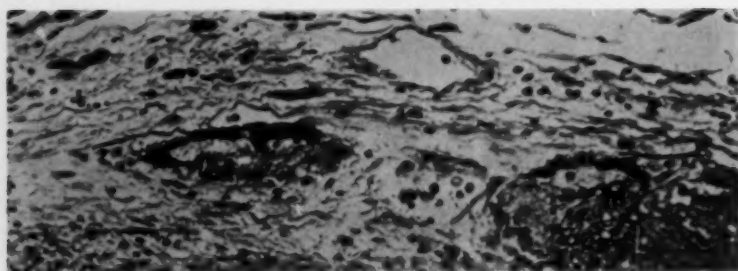


Fig. 15 (Geeraets and Guerry). Defects in Bruch's membrane and degeneration of the pigment epithelium. Proliferation of connective tissue and new-formed capillaries penetrate through both Bruch's membrane and pigment layer (Verhoeff-van Gieson, $\times 130$).

exudates had separated the remaining retinal layers entirely. Iron staining demonstrated hemosiderin crystals in macrophages but Bruch's membrane did not stain blue as has been described by Hagedoorn in eyes with angioid streaks.

The choroidal veins and arteries did not show abnormal changes, but the long ciliary arteries and one ciliary vein did show some pathology (fig. 16).

In three of the long ciliary arteries, the tunica elastica interna was interrupted and in some places doubled. Some increase in connective tissue was found in the same areas of the vessel wall where the changes in elastic tissue were present. Thickening of

the intima did not exist. In several sections loosening of the intima of a ciliary vein was found, with hemorrhages between the layers of the vessel wall and within the surrounding tissue. Staining with Alcian blue for acid mucopolysaccharides and PAS in regard to obtaining certain information on the biochemistry did not show any staining. These negative results may be due to rapid changes post mortem and are hence not significant. But it should be of interest to do further studies in this direction.

COMMENT

The occurrence of angioid streaks in association with pseudoxanthoma elasticum is

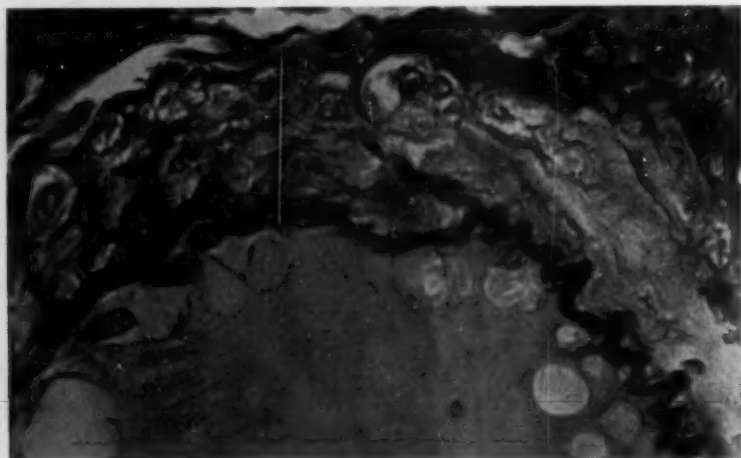


Fig. 16 (Geeraets and Guerry). Doubling and splitting of the lamina elastica interna of a long ciliary artery (Verhoeff-van Gieson, $\times 150$).

well known. The incidence of such fundus changes in this generalized disease of the elastic tissue is recorded as somewhat between 40 and 60 percent. Except for this condition, which is in itself very rare, angioid streaks have been described as occurring in a number of other diseases, but these are ophthalmologic rarities. Therefore, the occurrence of angioid streaks in almost six percent of the eyes of patients with sickle-cell disease can be considered as exceptionally high. Since angioid streaks, in general, are a rarity, it would seem that their combination with sickle-cell disease cannot be regarded as a mere coincidence but that instead there is a definite relationship. In addition it is of interest to note that only in one patient was pseudoxanthoma elasticum present clinically. Although no skin biopsies were performed, it is unlikely that pseudoxanthoma elasticum could have been present without being clinically demonstrable.

While the clinical observation of angioid streaks reported here can be considered as an established fact, the histopathologic findings described call for further comparison. It should be repeated that the histopathology discussed here was observed in eyes which presented funduscopically sickle-cell retinopathy but no angioid streaks. Therefore the similarity between certain pathologic changes in these sections and those found in angioid streaks is very interesting.

The response of Bruch's membrane to elastic tissue staining was strikingly similar. In both—angioid streaks and the eyes described here—large areas, mainly in the posterior part of the globe, did not stain with orcein or Verhoeff's elastic tissue stain. In the periphery usually normal staining ability was present in both. In both conditions, defects in Bruch's membrane were found to be of different width and with sharp cut edges of Bruch's membrane at the margins of the defect (fig. 5).

Both conditions leave the pigmented epithelium unimpaired in areas of smaller defects in Bruch's membrane, but show de-

generative changes where larger defects are present (figs. 7 and 15). Separation of Bruch's layer and the basal layer of the pigmented epithelium were reported in angioid streaks and were also found in this study. In both, an accumulation of colloid material was located between these two structures, forming excrescences on Bruch's membrane (fig. 6).

In eyes with angioid streaks as well as in our specimens, proliferative tissue derived from the choroid penetrated through both—Bruch's layer and the basal layer of the pigmented epithelium—separating the remaining retinal layers. (fig. 15). A destruction of the rods and cones in some areas was found by Böck in his study on angioid streaks and was also found in some of our sections (fig. 11).

A positive staining of Bruch's membrane with iron stain, as described by Hagedoorn, of eyes with angioid streaks could not be demonstrated in our study. But this finding depends upon the previous fixation method of the specimens and was also negative in Böck's studies on angioid streaks. Furthermore, the reported changes on the lamina elastica interna of one choroidal artery by Böck and on the long ciliary arteries by Böck and Hagedoorn were found to be similar to those observed in our sections (figs. 12, 13, 14, and 16).

Vasoproliferation and new vessel formation in the retina associated with congested veins and intravascular sickling as observed in our sections can be regarded as a general finding in all organs of sickle-cell patients. Also the numerous small areas with hemosiderin conglomerations as described in the choroid are usually found in most of the organs, particularly in the spleen, liver, kidneys and digestive tract.

In regard to these observations, three main questions arise:

1. Can sickle-cell disease, as a generalized disorder, cause destruction of elastic tissue in the eye or in other organs of the body?

2. Do angioid streaks develop secondary

to the local pathology of sickle-cell retinopathy?

3. Since sickle-cell disease and Groenblad-Strandberg syndrome are well-known hereditary diseases, is the occurrence of angioid streaks in sickle-cell disease familial?

The generalized clinical and pathologic findings in patients suffering from sickle-cell disease certainly suggest the possibility of destruction of preselective tissue. The constant low oxygen tension combined with intravascular sickling and stasis may explain the involvement of the elastic fibers in the vessel wall. Hemorrhages, neovascularization and microaneurysms which occur frequently in this disease may be regarded as evidence confirming the fact that the vascular system participates in the pathology.

The assumption that angioid streaks—as a symptom of a generalized elastic tissue degeneration—are caused by a nutrient factor might also be applied in sickle-cell disease. Since Bruch's membrane does not consist of any cells but has only protoplasmatic prolongations which extend into the choriocapillary layer (fig. 17), it was thought

(Hagedoorn) that the distance of Bruch's fibers from their nutrient cells might well be the cause of the destruction of this layer. This theory fits sickle-cell disease even more aptly, since, in addition to the anatomic peculiarity, there is a definite disturbance in the metabolic exchange. With prolonged stasis and occlusion of the choriocapillaris, and with the potential factor of a constant low oxygen tension, the nutrition may even be more impaired in this disease.

As a result of such nutritional damage, variation in ocular pressure, such as that caused by extraocular muscle activity, respiration, pulse, and so forth may result in ruptures of Bruch's membrane. This theory was mentioned by Hagedoorn who compared the compensatory action of Bruch's membrane in the eye with the action of the elastic fibers in skin areas of greater mechanical irritation. In this way he explained the pathologic findings in pseudoxanthoma elasticum and angioid streaks as being located in areas of greater stress.

With the clinical and pathologic picture of sickle-cell disease in mind, the ocular find-



Fig. 17 (Geeraets and Guerry). Protoplasmic prolongation of Bruch's membrane between the choroidal capillary layer (Hematoxylin-eosin, $\times 600$).

ings as described here seem more likely to be a part of systemic manifestations. But since angioid streaks have been reported in such conditions as ocular inflammation and injury, one must also consider their occurrence in sickle-cell disease to be secondary to the local primary changes of sickle-cell retinopathy.

As has already been pointed out, there are typical and significant fundus changes in sickle-cell disease, depending on the severity of the generalized disease. It is entirely possible that such eyeground changes—consisting of ischemic retinal areas, neovascularization and microaneurysms of retinal venules, pre-, intra- and subretinal hemorrhages, choroidal atrophy, retinitis proliferans, and so forth—might result in destruction of Bruch's membrane. But with the associated findings of lesions in the elastic layer of the long ciliary arteries, and in other organs, it seems more likely to us that angioid streaks in patients with sickle-cell disease are part and parcel of a generalized systemic manifestation.

Further studies of the elastic tissue of other organs in sickle-cell disease are now

being done, as well as biochemical studies on enzymatic action and elastase inhibitors.

SUMMARY

The relatively high incidence of angioid streaks in patients with sickle-cell disease is discussed. This ocular pathology was noted in six-percent of a group of 69 cases.

The clinical, histopathologic and laboratory findings in angioid streaks and sickle-cell disease are reviewed.

Funduscopy examinations on sickle-cell patients presenting angioid streaks are described. Histopathologic findings of eyes from patients with sickle-cell disease are compared with those reported in angioid streaks.

A possible causative relationship between sickle-cell disease and elastic tissue pathology is suggested.

Further studies on this subject are in progress.

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EFFECTS OF PHOSPHOLINE-IODIDE (217MI) ON INTRAOCULAR PRESSURE IN MAN*

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The treatment of simple glaucoma has shown a considerable trend back toward the conservative management of the disease.

Cholinesterase inhibitors have been used in the control of the intraocular pressure for many years, starting with physostigmine (Eserine) which was obtained from the Calabar bean and was found to reduce the intraocular pressure as early as 1875.¹ Since then the search for more potent, less toxic, longer-acting cholinesterase inhibitors has continued. Within recent years a number of very potent cholinesterase inhibitors have been evaluated in the treatment of glaucoma. The first of these was isopropyl fluorophos-

phate (DFP)² and more recently demecarium bromide³ and others. Leopold⁴ described the use of phospholine iodide (217MI) in the treatment of glaucoma and Becker⁵ reported on its effect on aqueous outflow.

Phospholine iodide (217MI) is the quaternary form of thiophosphate and is a white crystalline water-soluble compound.⁶ It deteriorates without refrigeration, losing about 40 percent of its activity in half a year.⁴ The drug can be used in a 0.1, 0.25 and 0.5-percent solution into the conjunctival sac. As accumulation of acetylcholine takes place which in turn produces miosis, some spasm of accommodation, vasodilatation of conjunctival vessels, and an accompanying drop in intraocular pressure.

The present study was carried out to test

*From the Glaucoma Clinic, University Hospital. Phospholine iodide (217MI) kindly supplied by Campbell Pharmaceutical Company, New York.

the effect of phospholine iodide (217MI) on normal human eyes and to ascertain its hypotensive effect on glaucomatous eyes.

NORMAL EYES

A. METHOD

The group of patients with normal eyes were admitted for the treatment of conditions other than glaucoma, both in the eye department and in other departments of the hospital. Glaucoma was excluded by tonography, diurnal tension curves, examination of the fundus and visual field studies. Tonography was carried out with a Mueller electronic tonometer and a Honeywell-Brown recorder and was corrected, when necessary, for scleral rigidity which was estimated with the applanation tonometer and a 10-gm. Schiötz weight using the 1955 Friedenwald calibration throughout. A drop of 0.25-percent phospholine iodide was instilled in one eye only and three-hour tension checks were carried out during the day with a final reading at 10:00 P.M., the first morning reading at 6:00 A.M. Tonographies were carried out at 24-hour intervals and the study was continued until the effects of the drops had worn off. The patient's other eye acted as a control.

B. RESULTS

Five eyes of nonglaucomatous patients had one drop of 0.25-percent phospholine

iodide instilled into one eye. All eyes treated with 0.25-percent phospholine iodide showed a very pronounced fall in the intraocular pressure. The untreated eyes, which served as a control, showed no more than the daily diurnal variation in pressure. The intraocular pressure started to fall after about 12 hours following the instillation of drops but miosis was noted within half an hour and was maximal after about one hour following the instillation of the drops. There was frequently a slight rise of pressure amounting to 2.0 to 3.0 mm. Hg prior to the hypotensive phase. The average percentage fall of pressure in the five normal eyes studied was 55 percent, whereas the nontreated eyes had an average fall of 3.13 percent during the same period of time. All the treated eyes revealed a considerable increase in the facility of outflow (C) the average increase being 89 percent. The untreated eyes revealed a very slight decrease of facility of outflow during the same period of time. The results in the five normal eyes reported are tabulated in Table 1 and Figures 1 and 2.

Two normal patients had a drop of 0.1-percent phospholine iodide instilled into one eye but only one of those two showed a fall in the intraocular pressure of 33 percent, the other showed no effect at all. It is to be noted that in the patient who showed the response to the lower concentration of phospholine iodide the facility of outflow (C) showed some increase.

TABLE 1

EFFECT OF 0.25-PERCENT PHOSPHOLINE-IODIDE ON INTRAOCULAR PRESSURE IN NORMAL EYES

	Intraocular Pressure (mm.Hg) of Eye Treated		Intraocular Pressure (mm.Hg) of Untreated Eye at the Same Times		C* of Treated Eye		C* of Untreated Eye at the Same Times	
	Before	After			Before	After		
1	12	8.5	10.5	10	0.24	0.44	0.28	0.26
2	20	7	19	15	0.20	0.30	0.32	0.29
3	20	7	20	19	0.30	0.52	0.17	0.20
4	17	7	15	16	0.32	0.56	0.30	0.27
5	12	6	13	15	0.21	0.29	0.19	0.17
AVERAGE	16	7.1	15.5	15	0.25	0.47	0.25	0.24
% CHANGE	-55%		-3.3%		+89%		-4%	

* c.mm./min./mm.Hg

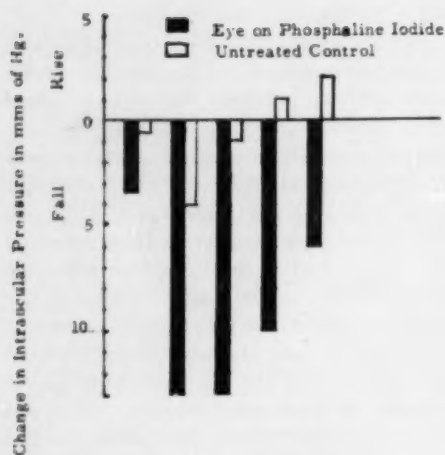


Fig. 1 (Drance and Carr). Effects of 0.25-percent phospholine iodide (217MI) on the intraocular pressure in five nonglaucomatous eyes.

C. SIDE-EFFECTS

Miosis commenced within half an hour in the treated eye, the pupils became pinpoint and remained miotic for a longer period of time than the ocular hypotension. All treated eyes showed a fair amount of conjunctival vasodilatation. The patients had some blurring of vision due to changes in their refractions toward myopia. Most patients complained of some headache in the overlying brow.

GLAUCOMATOUS EYES

A. STUDY

Fifty-nine nonoperated eyes with chronic simple glaucoma, in white patients, were treated with 0.25 and 0.1-percent phospholine iodide. Most patients were started on the drug because of failure to control intraocular pressure with more conventional miotics with or without the addition of carbonic anhydrase inhibitors. A few patients were started on phospholine iodide when the diagnosis of glaucoma was first made.

Eyes with angle-closure glaucoma were not included in this study because experience with similar drugs suggested some danger in

using these drugs in the angle-closure form of the disease.

All patients studied were in the hospital for diurnal pressure studies and stabilization. The fall of intraocular pressure recorded was the maximal reduction of intraocular pressure attained at equivalent times of day. Tonographic studies were carried out at frequent intervals.

The present study was only concerned with the hypotensive effects of phospholine iodide in glaucomatous eyes and was not intended to deal with the problem of long-term control of this condition which will form the substance of a separate report.

B. RESULTS

Fifty-seven of the 59 eyes treated with phospholine iodide showed a satisfactory drop in the intraocular pressure. The two eyes which failed to respond to the drug were both in the same patient and no explanation can be given for the failure of the drug to act. Figure 3 illustrates the fall of intraocular pressure in the individual eyes tested. The average percentage fall of intra-

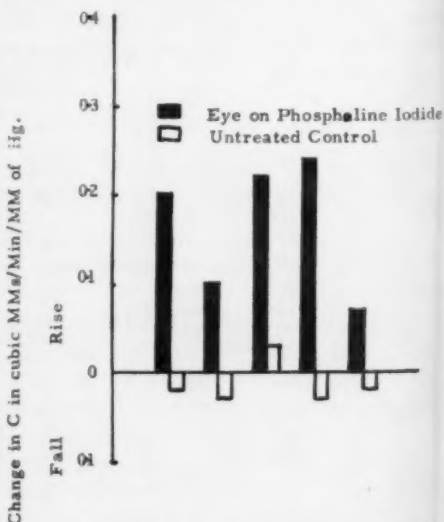


Fig. 2 (Drance and Carr). Effects of 0.25-percent phospholine iodide (217MI) on the facility of outflow (C) in five nonglaucomatous eyes.

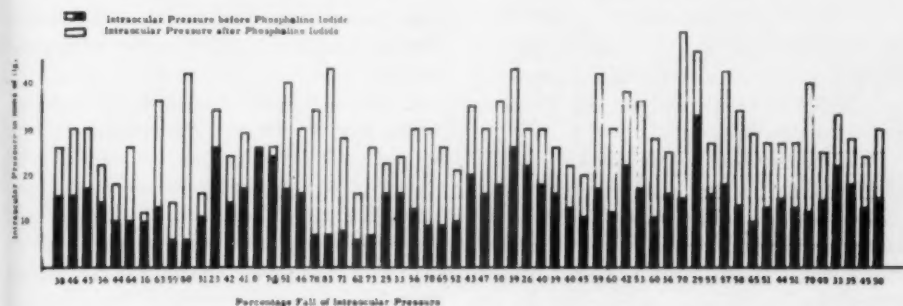


Fig. 3 (Drance and Carr). Effects of phospholine iodide on intraocular pressure in 59 eyes with chronic simple glaucoma. The changes in intraocular pressure are shown in mm. Hg and also as a percent fall of pressure.

ocular pressure in the 59 eyes was 48 percent. Satisfactory tonographic studies were carried out on 28 of the 59 eyes studied and the average increase in the facility of outflow (C) was 127 percent. The tonographic changes are graphically recorded in Figure 4.

C. SIDE-EFFECTS

The side-effects in the glaucomatous group of patients were identical with those already described for normal eyes. It was found that 0.5-percent phospholine iodide caused fairly considerable local symptoms and this strength of preparation was not

used in the later part of the series. It is to be noted that two patients, after the instillation of only one drop of 0.25-percent phospholine iodide, developed severe epigastric cramps, nausea and vomiting, cold sweats and a general feeling of prostration. These symptoms were rapidly cleared up with subcutaneous injections of 1/100 gr. of atropine sulfate. The local side-effects around the eye only rarely necessitated cessation of therapy. The long-term tolerance of patients to phospholine iodide will be discussed in the paper dealing with the long-term control of glaucoma with this drug.

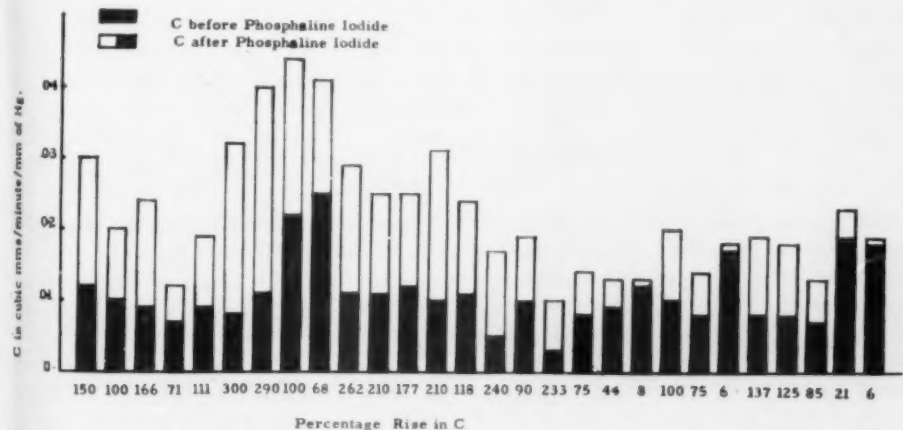


Fig. 4 (Drance and Carr). Effects of phospholine iodide on facility of outflow (C) in 28 eyes with chronic simple glaucoma. The changes in (C) shown in c.mm./min./mm. Hg and also as a percent increase of facility of outflow (C).

SUMMARY

1. The effects of a new, synthetic, powerful cholinesterase inhibitor phospholine iodide (217MI) on the intraocular pressure in man are described.

2. In the normal human eye phospholine iodide produced a very marked fall in intraocular pressure which came on about 12 hours after instillation and persisted for approximately three to five days. Tonographic studies revealed a marked increase in the facility of outflow (C).

3. Of 59 eyes with chronic simple glaucoma, 57 showed a significant and considerable drop in the intraocular pressure after instillation of 0.25-percent phospholine iodide.

4. Of 28 eyes with chronic simple glaucoma, 24 showed a considerable increase in the facility of outflow (C) on tonographic studies. All four eyes which failed to show

any increase in the facility of outflow showed a significant fall in the intraocular pressure.

5. The hypotensive action of phospholine iodide was accompanied in a majority of normal and glaucomatous eyes by intense miosis, some spasm of accommodation, vasodilatation of the conjunctival vessels and headache in the brow overlying the treated eye. The unpleasant side-effects seemed to wear off with continued use of the drops.

Two glaucomatous patients showed very definite systemic disturbances following the use of local phospholine iodide which were reversed by systemic atropine sulfate.

University Hospital.

I wish to thank Miss Bower for helping with the graphs and illustrations and Mr. B. Cook for his untiring efforts of obtaining the nocturnal tensions and to the many patients who have co-operated in obtaining the necessary data.

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OPHTHALMOSCOPICALLY VISIBLE SMALL SPOTS IN THE OCULAR FUNDUS*

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The first stereoscopic photographs of the fundi oculi were made by me more than 30 years ago. Some of them were included in my 1929 *Atlas*. Since that time I have had many demonstrations and published another *Atlas* of color photographs. This presentation is new.

* Presented at the 95th annual meeting of the American Ophthalmological Society, Hot Springs, Virginia, May, 1959. Every spot was illustrated by a Kodachrome photograph.

Spots, small parts differing in color, finish, or material from the main part of the fundus may be sufficiently characteristic in form, distribution and life cycle to assist materially in the clinical diagnosis.

The most distinctive is blood, which when enclosed in a dilated portion of a small vessel is a microaneurysm. Ballantyne first reported it as a pathognomonic sign of diabetes. This was soon disproved for in many other conditions aneurysms are present.

A typical microaneurysm is a small, smooth-surfaced, red globe usually emanating from a small artery. It grows slowly, rarely disappears spontaneously and when once established is always in the same place. This was well seen in a 63-year-old woman who was known to have had diabetes for two years. An aneurysm photographed over a period of many months showed no alteration in size, color or location.

In a case of congenital, multiple, gross retinal vessel aneurysms, which looked like a huge bunch of grapes, small and definitely globular microaneurysms were found about the outer edges.

On a large, irregularly quadrate, macular region mass of Coats' exudative choroiditis there were several, isolated microaneurysms and also some on different sides of a major vessel.

In hemorrhage the color varies from pale red to dark, almost black. A small retinal hemorrhage rarely has the smooth surface of an aneurysm and if followed long enough under proper conditions always shows either an increase or decrease in size.

In contrast to blood or aneurysm there are pale sometimes translucent, or yellowish spots beneath the retinal vessels, they may be few, scattered about the posterior pole, form a complete layer over the fundus, be widely separated or closely packed together as round or ovoid, confluent elevations. These are commonly called drusen, colloid bodies in Bruch's membrane, and as the illustrations show are easily identified by their location and color. In the elderly, they may be almost white, several large vessel diameters in size, and irregularly pigmented, the characteristic Tay's choroiditis.

Scores of reports in the literature calling attention to tapetoretinal degeneration have led to much confusion. François in his excellent address before the Section on Ophthalmology of the American Medical Association stated that the "tapetal reflex which is probably due to an irregularity in the thickness of the vitreous membrane, is not asso-

ciated with any deficiency of vision."

Ida Mann writes: "In man no tapetum is normally present, but in very rare instances a tapetal-like reflex has been noticed." Her two illustrations are similar to colloid degenerations and in neither case was there nightblindness. Further she states that: "It is possible that both these cases represent a congenital abnormality of the membrane of Bruch." Her report coupled with the study of stereoscopic photographs strongly suggests that human "tapetoretinal degeneration" is a type of Bruch's membrane colloid deposits.

It may be that large spots of greater thickness, more irregular distribution and seemingly deeper in the fundus, alluded to as choroidopathy, are pathologically similar to the ordinary drusen although visual disturbances are greater.

White spots in the fundus may be few or so numerous as to cover the entire visible background, associated with nightblindness and pigmentations usually of bone corpuscle shape. The age at discovery is variable.

A woman who died when she was 81 years of age had been observed for 40 years. The original dominant feature of her fundi was the great number of separate, white spots beneath the retinal vessels. As time passed the discrete spots disappeared in areas of choroidal atrophy with branched pigmentations in the equatorial and peripapillary regions. She had always been nightblind. This is the classic picture of retinitis punctata albescentis with retinitis pigmentosa.

It is probable that the majority of such cases progress through all phases of retinitis pigmentosa with field changes, decreased central vision and an overshadowing of the white spots by the greater choroidal involvement.

In a patient without nightblindness the white spots were fewer, new ones developed more slowly and pathologic pigmentations did not develop during several years of observation.

A 12-year-old-girl was nightblind with a

peculiar, gray-green background of small light colored, not white, spots forming a complete sheet over the fundus with scattered amorphous pigmentations.

The female type of choroideremia consists of dark, almost black, spheroidal spots in the equatorial zone with nightblindness. The pigmentations slowly increase.

Soft-edged, lightly pigmented, rounded areas found in conjunction with malignant melanoma of the choroid suggest metastases by their distribution about the tumor and increase in size as the growth enlarges.

Flat hemorrhages in malignant melanoma vary in size and density and may be a cause of sudden reduction in vision.

The dispersion of pigment in some phases of exudative senile macular disease ranges from minute, comparatively thin specks to those several times the width of a primary retinal vessel. They may become measurably smaller and lighter in color, but usually they or small deeply placed hemorrhages are the earliest signs of what develops into extensive degenerations.

In traumatic retinochoroiditis the areas of pigmentation are usually dark or black, small or even large plaques, which increase in size and number for a time after the injury and then become stationary for the rest of life. Rupture of the choroid is a common cause.

Prolific sources of yellowish white and whitish yellow spots in the fundus are dia-

betes, nephritis, and hypertension.

The yellow white spots of a diabetic retinopathy have been described for years. They may start as small dots and become large masses accompanied by hemorrhages at any stage from early to late. The retinopathy usually appears in those who have had diabetes for years and have been under "control" by diet, insulin, or the new drugs. The well-known pattern of small hemorrhages, exudates and microaneurysms is so suggestive of a diabetic origin that the tentative diagnosis is often given when the first ophthalmoscopic examination is completed.

After sudden occlusion of the central vein delicate, minute, yellow dots may be among the late signs of resolution.

In nephritis the spots may be soft, gray white edemas, ischemic areas or arranged in stellate groups about the macula. Those in hypertension are always accompanied by visible retinal vessel alterations.

Cholesterin crystals are so easily recognized by their brilliant iridescence that no other description is needed.

The congenital choroidal pigmentations are flat, irregular in outline and variable in size with the larger ones nearer the equator and the small toward the disc; they seem to remain unchanged by time and cause no decrease in sight.

344 State Street.

OCULAR COMPLICATIONS OF TRANSSPHENOIDAL YTTRIUM-90 HYPOPHYSECTOMY*

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Some cancers which arise in the male or the female breast, or in the prostate gland, are of sufficient maturity to be functionally dependent upon the same endocrine substances as the cells from which they arise. Thus, according to Huggins,¹ their growth

may be either inhibited or stimulated by withdrawal or administration of the hormonal compounds required for their meta-

cer Research Hospital, The University of Chicago. Preparation of this report was aided in part by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago. Read at the 95th annual meeting of the American Ophthalmological Society, Hot Springs, Virginia, May, 1959.

*From the Department of Surgery (Ophthalmology and Otolaryngology) and the Argonne Can-

bolic activity. Such hormonal-dependent cancers can be sustained and propagated by endocrine function which is not abnormal in kind or exaggerated in rate but which is operating at a normal or even a subnormal level.

Removal of the hormonal element in carcinoma of the prostate may be achieved by orchiectomy, which removes the principle source of prostatic stimulating hormones. The same thing may also be accomplished by administration of phenolic estrogens which cause depression of the pituitary gonadotrophins. At present the most effective control of metastatic carcinoma of the prostate is achieved by orchiectomy combined with the administration of estrogens.

Sir George Beatson,² in 1896, postulated that mammary carcinomas were due to "ovarian irritation" and empirically demonstrated dependence on ovarian hormones in two patients who had regression of breast cancer following oophorectomy. The contemporaneous development of ovarian radiation, which is slower and less certain of eliminating ovarian function than the surgical method, led to a decline in surgical oophorectomy for this purpose.

Hormones which sustain mammary cancer are formed, in addition to the ovary, in the adrenal cortex which hypertrophies after removal of the gonads. Huggins proposed therefore that bilateral adrenalectomy be combined with castration to remove the dual source of the hormones controlling breast cancers. The development of the hormones to combat the surgically induced adrenal insufficiency has led to widespread application of these principles in the therapy of metastatic mammary carcinoma.

In 1952, Luft, Olivecrona and Sjögren³ logically extended this reasoning, and reported surgical hypophysectomy to remove the stimulus to ovarian and adrenal cortex secretion to achieve endocrinologic control and palliation of hormonal-dependent advanced carcinoma of the breast and prostate. Many of the patients with metastatic cancer

who require this method of therapy are severely debilitated and the requirement that the surgery be minimally distressing to such patients has led to a wide variety of techniques for excising or destroying the pituitary gland.⁴ In addition to surgical excision, methods for destroying the gland by the introduction of radioactive gold or radon into the sella turcica have been described. Generally the use of an isotope emitting gamma rays must be considered undesirable because of the widespread necrosis caused. The gland can be ablated by high doses of an externally administered proton beam; ordinary external roentgen therapy does not yield sufficiently energetic radiation to destroy the pituitary.

In 1953, Rasmussen, Harper and Kennedy,⁵ at the University of Chicago, suggested that radioactive yttrium beads implanted in the sella turcica would destroy the pituitary gland and used the transcranial approach for placement of the radiation source. The operation results in 45 patients operated by this route have been reviewed recently by Evans and his co-workers.⁶

Forrest and Peebles-Brown,⁷ in 1955, at the University Department of Surgery of the Western Infirmary, Glasgow, described a technique of implanting radon in the sella turcica by means of two cannulas inserted through the nose and sphenoidal sinus. Forty-five patients were treated and of these, seven developed visual field changes. Harrington⁸ has recently described these changes which occurred from one week (two patients) to one year (one patient) after the procedure. Because of this complication, radioactive yttrium has been substituted for radon by these workers. Harrington found four of 55 patients with visual loss with this procedure, all nonprogressive and not disabling, and does not mention ophthalmoplegia as a complication.

Radioactive yttrium is familiar to ophthalmologists as the therapeutically effective product of decay of radioactive strontium. Yttrium-90 decays to stable zirconium by

emission of a beta particle with a maximum energy of 2.3 million electron volts and a mean energy of 0.90 million electron volts. The penetration in tissues is maximally about 9.0 mm. and necrosis is evident at only about 4.0 mm. distance. The area of necrosis is sharply delineated. The half-life is 62 hours and in the form used at the University of Chicago it has an activity of about 0.5 mc. per milligram of yttrium oxide. Beads used in the study were those described by Kisieleski, Svihla, and Brues⁹ to deliver discrete sources of beta radiation. The effects of these beads when applied to the posterior ocular segment have been described by Newell, Harper and Koistinen.¹⁰ The beads are manufactured by compressing yttrium-90 oxide powder in a mold and then sintering the material in an alumina crucible at 1,650°C. for one hour which converts the beads to solid ceramic material. Activities of 1.0 to 2.0 mc. per pellet are obtained by placing them in a thermal neutron flux of three times 10^{18} N/cm.²/sec. for four to five hours.

From the experimental work of Marinelli, Quimby and Hine¹¹ it was believed the complete destruction of the pituitary was more likely to follow the implant of multiple discrete radioactive sources, 1.0 mm. by 2.0 mm., rather than two large sources, 2.0 mm. by 6.0 mm., used by Forrest and his associates. Implantation of the radioactive source through the nose had two main advantages: a lower operative mortality rate than the transcranial approach, and the avoidance of general anesthesia, which is a considerable advantage in severely debilitated patients.

The technique of implantation of the beads has been described in detail elsewhere.¹² A specially constructed 17-gauge needle containing the radioactive yttrium pellets is passed into the nostril and guided by direct vision to the anterior wall of the sphenoid sinus. By means of axial and lateral image amplifier tubes a radiologist directs the placement of the needle into the sella turcica where the beads are deposited. Gen-

erally, eight beads are implanted but as many as 11 and as few as six have been used. Usually the needle is first advanced to the medial portion of the left half of the pituitary and a posterior bead deposited. The needle is then withdrawn a few mm. and an anterior bead deposited. The needle is then withdrawn into the sphenoidal sinus and angled laterally before being advanced again to deposit beads in the anterior and posterior areas of the lateral portion of the gland. A similar maneuver is repeated on the opposite side.

Postoperatively all patients require replacement therapy with cortisone. Hypothyroidism develops after two or three months and thyroid extract may be required. Damage to the closely associated hypothalamus causes diabetes insipidus which necessitates the administration of posterior pituitary extract, usually by nasal insufflation.

During the period of June, 1957, to January, 1959, a total of 70 patients with metastatic carcinoma were treated by trans-sphenoidal implantation of yttrium-90 in the pituitary gland. The sex distribution and primary tumor are listed in Table 1. There were 60 female and 10 male patients. Two of the female patients had metastatic carcinoma of the ovary and the remainder had metastatic carcinoma originating in the breast. Eight male patients had metastatic cancer of the prostate, one had metastatic carcinoma of the breast, and one had metastatic carcinoma of the parathyroid gland.

The youngest patient was 29 years of age and the oldest 73 years. There is no evidence that patients must be in the age group of presumable maximal endocrine activity in

TABLE 1
SEX AND ORIGIN OF PRIMARY TUMOR

Male	10
Prostate	8
Parathyroid	1
Breast	1
Female	60
Ovary	2
Breast	58

benefit from the procedure and thus advanced age in itself is not a contraindication to the procedure. Indeed in the nine patients aged less than 39 years treated by this method there was no improvement with the procedure. Unfortunately there is no method at present of learning prior to hypophysectomy whether or not the malignancy is of the type to respond favorably to the procedure.

Improvement, when it occurs, may be divided into a subjective and an objective response. Subjective improvement consists largely of relief of pain, or increased sense of well-being. Such factors are notably difficult to evaluate and may often be of psychogenic origin. Subjective improvement not uncommonly occurs although the cancer continues to develop.

Objective improvement may consist of either arrest of progression of the disease, or regression. Arrest may be defined as failure of the cancer to progress as indicated by no new lesions developing and no increase in size of existing areas of the disease. Regression includes radiographic evidence of sclerosis of osteolytic bone lesions without either the development of new areas or the progression of existing sites. A decrease in size of either palpable tumors or radiographically or ophthalmoscopically visible tumors without development of additional lesions may occur with regression. This may be associated with absorption of ascites fluid or a pleural effusion. Biochemical evidence of regression is a decrease in elevated blood calcium and urine values and a decrease in alkaline and acid phosphatase values.

Fifty-nine of the 70 patients treated by this method had metastatic carcinomas of the breast. The experience with the remaining 11 patients is too diverse to yield worthwhile analyses of the results. No patient aged less than 39 years experienced improvement. Of the patients with breast cancer there was no improvement in 34, or 57.6 percent, and benefit in 25, or 42.4 percent. Thirteen of the 25 patients with improve-

ment experienced arrest only and in the remaining 12 regression was observed.

The effect of the procedure on survival is difficult to analyze because the disease was so far advanced when the patients were hypophysectomized. In those patients without therapeutic response, death occurred on an average of 3.6 months later. In patients with arrest of the disease, death occurred on an average of eight months later, with extremes of two and 12 months. Two patients are still alive five and eight months respectively after the procedure. In the four patients with regression who have died, death occurred at an average of 14 months after the procedure, with extremes of five and 20 months. Eight of the 12 patients with regression have survived for periods of eight to 20 months after the hypophysectomy.

Nine patients had adrenalectomy combined with oophorectomy prior to hypophysectomy. Four showed no response, four demonstrated arrest, and there was regression in one. However, the patient with regression and one of the patients with arrest had hypophysectomy within a week of the adrenalectomy and oophorectomy, so that the cause of the beneficial effect is not known.

The complications observed following the procedure are shown in Table 2. Many of the patients experienced more than one complication. Death occurred due to progression of the disease within 30 days of the operative procedure in 10 of the 70 patients. Many of the patients subjected to the procedure had far-advanced metastatic disease, so severe in several that they were unable to sit up so as to measure vision preoperatively.

TABLE 2
COMPLICATIONS ENCOUNTERED IN
YTTRIUM HYPOPHYSECTOMY

Ocular muscle weakness	23 (32%)
Optic atrophy	2
Anesthesia of face	1
Rhinorrhea (CSF)	14 (20%)
Meningitis	8 (11%)
Diabetes insipidus	31 (44%)

51 (73%) patients developed one or more complications.

One of the patients dying within this period had a rhinorrhea without evidence of intracranial infection. None of the remaining patients dying within 30 days had a rhinorrhea or intracranial infection or hemorrhage, the chief fatal complications to be ascribed to the operative procedure.

Death in three patients may be ascribed to the operative procedure, although none occurred in the first month following surgery. Two of these deaths were due to meningitis following rhinorrhea. The third death arose from damage to the hypothalamus, due to a bead being implanted in the structure above the diaphragma sellae.

Fourteen patients had a rhinorrhea and of these, eight developed clinical signs of meningitis. There was no radiographic evidence to indicate any particular pattern of placement of the beads to cause this complication. The rhinorrhea occurred sporadically and without reference to the location of the beads.

Diabetes insipidus occurred in 31 patients and was manifested by polyuria and polydipsia, relieved by nasal insufflation of posterior pituitary extract or the intramuscular injection of pitressin tannate. This complication indicates damage to the hypothalamus and is more annoying than disabling. The most disabling complication of the procedure arose from involvement of the motor nerves to the eye within the cavernous sinus. Each of the patients undergoing yttrium hypophysectomy had an ophthalmic examination preoperatively with central vision measurement and determination of the peripheral visual fields by means of the Harrington screening method. Ocular muscle balance and movements were tested grossly and ophthalmoscopic examination was done. A similar examination was performed prior to discharge from the hospital and again if the patient had ocular complaints. However, since many patients came from afar, this report presents the minimal rather than the maximal number of ocular complications.

The chief ocular complication was ocular

muscle palsy arising from involvement of the motor nerves. In nine patients there was isolated involvement of the third cranial nerve on one side. In an additional patient the third nerve was involved bilaterally. An additional eight patients had involvement of both the third and fourth cranial nerves. One patient had involvement of all the motor nerves on one side. In an additional four patients the sixth cranial nerve was involved. One of these patients had bilateral lateral rectus paresis, presumably from intracranial metastasis prior to the procedure, and the third nerve was involved postoperatively. It is possible that rarely this complication may have arisen from extension of the tumor rather than from damage to the nerve from the radiation. The paresis usually developed within one week of the procedure although on occasion it was observed to develop within two or three days and on one occasion after four weeks. Because of the 62-hour half-life of yttrium-90, delayed complications are not to be expected and the initial damage is also the maximal.

Ocular complications arising from the procedure occur because of faulty positioning of the beads near important intracranial structures. Kelly, et al.¹³ have demonstrated that pituitary tissue is relatively more resistant to radiation than other nervous tissue and the surgeon is thus confronted with the problem of depositing radioactive material within the gland with an intensity adequate to destroy it but not to place the material so close to motor nerves or the optic chiasm that damage will result. If implantation is made within four mm. of a nerve, the nerve will be damaged. The dosage of radiation required to cause damage to various structures is approximately 110,000 to 190,000 rep to the anterior lobe of the hypophysis, 60,000 to 120,000 rep to the hypothalamus, 60,000 to 140,000 to the optic chiasm or tract, and 30,000 to 60,000 rep to the oculomotor nerve. From these studies, in monkeys, it is evident that necrosis will occur in the third nerve with a radiation dosage which is insufficient

to damage immediately adjacent structures.

The anatomy of the pituitary gland and the surrounding structures has been extensively studied by Walsh¹⁴ and Weinberger, Adler and Grant¹⁵ in respect to ocular motor nerve involvement in the lateral extension of pituitary adenomas. The neural symptoms observed in the patient undergoing yttrium-90 hypophysectomy are essentially those of the syndrome of the cavernous sinus, described initially by Jefferson,¹⁶ arising from impairment of the function of the third, fourth, sixth and ophthalmic branch of the fifth nerves.

Nurnberger and Korey¹⁷ describe the cavernous sinus as a spongy trabeculated venous channel which passes from the superior orbital fissure to the level of the tip of the petrous bone. The sinus communicates with its mate, forming a circumsellar net with the pterygoid plexus and with the pericarotid venous plexus. According to Ralph¹⁸ a wide variation exists in the size and the arrangement of the cavernous sinuses and the ophthalmic veins in normal persons.

The sixth nerve passes within the inferior petrosal sinus under the petrosphenoid ligament to enter the body of the cavernous sinus where it lies lateral and inferior to the carotid artery. In the posterior portion of the cavernous sinus only the sixth nerve and the first and second divisions of the fifth nerve are present. Further forward in the sinus the sixth nerve becomes lateral and inferior. It enters the superior orbital fissure inferiorly and laterally; possibly because of its position along the base of the skull it is more protected from the effects of the radiation from beads.

The third nerve enters the wall of the cavernous sinus at the junction of the posterior and middle third. Gifford¹⁹ states that the third nerve usually divides into its upper and lower branches well back in the cavernous sinus opposite the ascending curve of the carotid artery.

The fourth nerve enters the wall of the sinus just posterior to and below the en-

trance of the third nerve. It is located in the lateral wall of the sinus and goes through the upper part of the superior orbital fissure after passing medial to the third nerve.

In the study of Weinberger, et al.¹⁵ the third nerve was most commonly involved in lateral extension of pituitary tumors. In case of partial palsy the disturbance ranged from ptosis to paresis of isolated movements. They stated that this appeared to be somewhat unusual since the accepted idea of paralysis of the third nerve is that peripheral lesions produce impairment of all functions of the nerve.

Authors who have noted the infrequent solitary implication of the sixth nerve have attributed it to the low-lying and sheltered position of the nerve in the cavernous sinus. However, the absolute as well as the relative position of the ocular nerves in the cavernous sinus are subject to considerable variability.

Ophthalmoplegia following yttrium hypophysectomy must be attributed to necrosis of motor nerves, most probably in the middle to anterior portion of the cavernous sinus. The likely explanation of such a complication is too lateral placement of a radioactive bead so that it is adjacent to the radiosensitive motor nerves. It must be noted that the anterior and posterior borders of the sella turcica are well-defined bony structures while the lateral borders are composed of soft tissue. Thus, while the placement of beads within the shadow of the sella turcica by means of the laterally placed image amplifier is quite accurate the placement by means of the axial image amplifier is done without the benefit of well-defined bony margins for guidance.

Involvement of the fifth nerve occurred in but a single patient who had a bead deposited far laterally. Denny-Brown and Brenner¹⁰ have described the fifth nerve as less susceptible to pathologic changes induced by pressure than motor nerves. A similar explanation may be valid for pathologic changes induced by radiation, although the lateral position of the fifth nerve in the cav-

ernous sinus makes involvement less likely.

A single case of involvement of the optic nerve was observed and there was no instance of demonstrable chiasmal damage. The infrequency of this complication is probably related to the accuracy with which radioactive pellets were deposited within the vertical confines of the sella turcica and thus not close enough to the optic chiasm to cause necrosis. Schaeffer²⁰ has shown that the space between the diaphragma sellae and the undersurface of the chiasm varied from a potential cleft to a vertical interval of 10 mm. There is additionally a wide variation in the relation of the optic chiasm to the sella turcica. Schaeffer found that the position of the chiasm directly above the sella occurred in but 12 percent of the bodies examined, although in 79 percent the chiasm lay wholly or partly above the sella turcica and hypophysis. In five percent of the bodies the chiasm lay anterior to the sella turcica, and in four percent it was located entirely behind.

DISCUSSION

The principles governing hypophysectomy to cause palliation or regression of hormonal-dependent metastatic cancer are well-established. To be widely useful the procedure must be minimally traumatic to the seriously ill patient and must assure elimination of all or nearly all of the functional pituitary gland.

At present, opinion is divided as to whether the best results can be achieved by transcranial hypophysectomy or by pernasal implantation of radioactive material. Unfortunately it is not possible to compare exactly the cumulative experience with the various procedures. Generally, patients in good enough physical condition to undergo transcranial surgery do not have disease as far advanced as those who must be subjected to less severe procedures. Nearly all agree that it is impossible to remove all of the gland consistently, irrespective of the implantation technique used. In this respect it

must be noted that partial removal of the pituitary gland is effective in causing hypothyroidism with a decrease in protein-bound iodine, decreasing gonadotrophins, and causing a decrease in 17-ketosteroid urinary excretion. Additionally, there may be beneficial effects on the carcinoma with partial removal. There is no diagnostic method of learning whether or not the whole gland is removed (provided a major portion is functionally inactivated) except histologic study after death. Thus far the reports concerning adequacy of removal or ablation are inadequate for analysis.

Implantation of a beta emitter within the sella turcica fulfills the criterion of minimal operative trauma. The number of complications arising with implantation of gamma emitters and the large area in which there is necrosis would seem to preclude their use.

The large number of complications arising with yttrium implantation is the chief indictment of the procedure. Fifty-one of the 70 patients experienced one or more complications, including, however, diabetes insipidus which may almost be considered an anticipated result rather than a complication. To learn if experience with the procedure reduced the incidence of complications the last 35 patients to undergo surgery were compared with the first 35. An insignificant decrease in complications was observed: 22 with complications in the second group, compared to 29 in the first group. Involvement of the motor nerves of the eye proved to be the most distressing complication to the patient and the surgeon. The paralysis was permanent in all patients, and the diplopia sometimes associated with the cosmetic defect of ptosis caused considerable discomfort to many patients.

Because of the many complications, the most serious of which were ocular, the method of hypophysectomy has been discontinued at the University of Chicago. At present the gland is being removed through a transantral approach.

SUMMARY

Seventy patients with advanced metastatic carcinoma have been treated by means of pernasal transsphenoidal yttrium-90 hypophysectomy. Of 59 patients with carcinoma of the breast beneficial results were obtained in 25 of whom 12 had regression of the disease. The chief ocular complication of the procedure was ocular muscle weakness arising

from radiation necrosis of the motor nerves within the cavernous sinus. The third nerve was involved the most frequently. Other complications included cerebro-spinal rhinorrhea complicated by late meningitis, diabetes insipidus, and single instances of optic atrophy and facial anesthesia.

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THE RADIOACTIVE PHOSPHORUS TEST IN OPHTHALMOLOGY*

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The use of radioactive phosphorus as a diagnostic aid in ophthalmology is well established. Numerous investigators¹⁻¹⁷ have contributed much significant material to the literature since 1952 in an effort to evaluate the test and devise a suitable set of criteria for the detection of ocular malignancy with this agent.

Over 500 tests were performed at the radiophosphorus laboratory of the Wills Eye Hospital since 1953. The study presented by Turner, Leopold, and Eisenberg¹⁰ in 1956 encompassed 262 of these cases. An additional 200 cases were reported by Carmichael and Leopold at the ninth annual Wills Conference in February 1957.¹⁸ This paper includes the latter 200 cases and the ones performed to date.

The original report from the Wills Laboratory by Eisenberg and co-workers⁷ discussed the reasons for the use of radioactive phosphorus as the isotope of choice for detecting intraocular neoplasms. It was also suggested that a variation of counts of more than 30 percent from the control eye should be considered a positive test for malignancy. A serious limitation to the value of the test appeared, in that inflammatory lesions also demonstrated an increased uptake of the isotope. Proceeding on the knowledge of the work of Jones and associates,¹⁹ Turner and co-workers modified the test so that counts would be made both at one and at 24 hours following the injection of radioactive phosphorus.⁸ It became evident on the basis of this work that the percentage difference in count dropped over a 24-hour period in inflammatory lesions and increased over a 24-

hour period in malignancy. Experimental evidence to support these statements has recently been presented.^{22, 23} The studies to be reported were performed with these criteria as a guide in each case except in the modification employed in iris lesions as will be noted later.

TECHNIQUE

The technique for the radioactive phosphorus tests includes simple precautions by the physician in contact with the isotope. The physician wears rubber gloves and a laboratory gown in the event that there might be spilling of the material on his hands or clothes. After the intravenous injection of 500 microcuries of radiophosphorus, the patient is instructed to wait approximately one hour so that the radiophosphorus may be transmitted throughout the entire vascular tree. Counts are then performed on the control eye at the 3, 6, 9, and 12-o'clock positions. This is done usually with the "anterior" probe which is a beveled Geiger counter tube (the "Anton 224"). In the case of posterior pole tumors, the curved posterior Geiger counter may be used (Anton 225 probe). The readings in each quadrant are of one-minute duration and an average of these counts is then obtained.

A number of counts may be made in each quadrant especially if the count variation appears to exceed 10 percent in any quadrant. If the count variation is stable, then additional counts need not be made.

The counter is placed over the area of the suspected pathology in the eye to be tested. A number of counts are made over this area and the region of highest uptake determined. Approximately four to six counts are performed in the area where the highest count

* From the Radioisotope Department of the Wills Eye Hospital.

is obtained. The formula $\frac{H-X}{x} \times 100 =$

"percentage greater or less than normal" is used where H = the average highest count in the pathologic eye and X = the average count of the normal eye.

Eisenberg, Leopold, and Sklaroff⁷ determined that the percentage greater than normal did not exceed 28. These workers therefore set their criteria for positivity at 30 percent. Counts are again repeated at 24 and 48 hours, if necessary. In the special

case of iris lesions a 48-hour count is often necessary.

RESULTS

A total of 291 cases have been studied at Wills Hospital since the previously reported work of Turner, Leopold and Eisenberg.¹⁰ These cases have been compiled since 1954. Of these 291 cases a total of 134 have been gathered in which pathologic study or successful surgical intervention was able to lend proof to the results of the tests. Table 1 shows distribution of these 130 cases.

TABLE 1
RESULTS OF P³² TEST IN ANTERIOR INTRAOCULAR LESIONS ACCESSIBLE TO THE
COUNTING PROBE

(Exclusive of retinoblastomas and posterior inaccessible lesions)

Investigator	No. of Eyes	Positive	Negative	False		Pathology of False Results
				Pos.	Neg.	
Donn & McTigue (1957)	35	16	17	1	1	(-) Malignant melanoma-iris (small) (+) Recent retinopexy
Dunphy, Dowling, Scott (1957)	31	18	11	1	1	(-) Malignant melanoma-iris (small) (+) Disciform degeneration
Palin, Tudway (1955)	13	8	3	1	1	(-) Malignant melanoma-iris (small) (+) Hemorrhage
Thomas, Krohmer, Storaasli (1952)	7	4	3	0	0	
Thomas, Krohmer, Storaasli, Friedhill (1954)	29	11	17	1	0	(+) Uveitis
Owens, King, Weils (1956)	15	11	2	2	0	(+) Recent retinopexy (+) Coats' disease
Turner, Leopold, Eisenberg (1956)	203	22	175	4	2	(+) Scleritis (+) Recent retinopexy (+) Vitreous hemorrhage—(not enucleated) (+) Absolute glaucoma & uveitis (not enucleated) (-) Iris melanoma (small) (-) Diktyoma
Kennedy, Glasser, Kazdan (1954)	21	9	11	1	0	(+) Intraocular hemorrhage (1 hr. reading only)
Carmichael Leopold, 1959*	134	24	105	2	3	(+) Benign adenoma of ciliary body (+) Macular hemorrhage (-) Three melanomas of posterior pole. Detection attempted by posterior probe
TOTAL	488	123	344	13	8	

Percent error 4.5 percent for anterior accessible lesions.

* 134 cases with pathologic follow-up or successful surgical intervention.

TABLE 2
CASES WITH PATHOLOGIC REPORTS OR
SUCCESSFUL SURGICAL RESULTS
(Total, 134 cases)

Serous and aphakic detachments successfully operated	Solid detachments
38	42
Uveitis with secondary glaucoma	Lid lesions
11	6
Granuloma of sclera	Orbital tumors
1	4
Vitreous hemorrhage	Iris lesions
6	18
Conjunctival lesions	
8	

Of the 134 cases, a total of 17 incorrect results were revealed. This total error results in an 86 percent accuracy of the test in all cases. However, eight lesions were not accessible to the anterior probe. If these cases were not included, then the accuracy of the test is definitely better than 90 percent. Continued experience has shown that the criteria set up by Eisenberg, Turner and Leopold⁷ are still acceptable for intraocular neoplasms. This set of criteria has been mentioned previously. Leopold²⁴ reported the results of P²² tests in anterior intraocular lesions compiled from a survey of the literature at a symposium on the diagnosis and management of intraocular melanomas (table 1). This table has been modified to include the present study. In the special study of iris lesions there is definite evidence that a change in the criteria may be necessary. Thirty-three iris lesions were studied in this series, 18 of which have had pathologic confirmation. Tables 2 to 7 are a resume of the cases to date.

It had been suggested that slowly metabolizing lesions such as isolated iris melanomas may have an initial low uptake with a 24-

TABLE 3
ACCURACY OF TEST IN ALL CASES

1. 17 incorrect results in 134 cases (86% accuracy)
2. 8 lesions not accessible to probe
3. Total accuracy when lesion accessible to probe—better than 90%

TABLE 4
SOLID DETACHMENTS ALONE

1. 11 incorrect results in 42 cases (74% accuracy)
2. Of these cases 8 lesions were inaccessible to the anterior probe
3. When lesion accessible to anterior probe the test is about 90% accurate

hour and possibly a 48-hour rise in count without resorting to the original 30 percent criteria. This was first tested on a case of Dr. Wilfred Fry and reported by him and discussed by Carmichael at the Philadelphia College of Physicians two years ago. In six of the 11 cases which have had pathologic confirmation the initial one-hour count was lower than 30 percent. However, the 24- and 48-hour counts continued to show a definite rise over the control eye so that eventually all showed a rise to or above 30 percent. Of the remaining eight cases all of which involved the angle or which were highly vascularized and involved the ciliary body, the counts were similar to those obtained with the usual intraocular melanomas. The significance of the results in these tests find support in the opinions of Zimmerman and Rones on the variable malignancy of iris lesions.²⁵

Results with the posterior probe for detecting posterior pole lesions have not been encouraging. It was anticipated that the probe as originally designed with a long curved handle and small flat tip would be able to slip readily behind the globe through a simple vertical or horizontal conjunctival incision beneath Tenon's capsule and between the extraocular muscles and come to rest over the lesion being tested. This could readily be accomplished under local pont-

TABLE 5
FALSE POSITIVES
(Seven cases)

A. Granuloma of sclera
B. Benign adenoma of ciliary body
C. Benign epithelioma of lid
D. Macular hemorrhage with posterior probe
E. Conjunctival nevi—2
F. Serous detachment—1

TABLE 6
FALSE NEGATIVES
(10 cases)

A. Malignant melanomas—9
1. Inaccessible to anterior probe—6
2. Posterior probe gave false negative in 3 cases
B. Orbital tumors—1
1. Lesion not accessible to probe

caine or cocaine anesthesia without marked discomfort to the patient.

The probe was passed blindly and the possibility of the probe lying directly over the lesion was questionable in all of the six cases in which it was employed. The total number of counts picked up by the probe in a one-minute interval was rather low in all cases, so that statistical evaluation of percentage difference was open to greater criticism than with the use of the anterior probe.

Dr. Adolph Vogel (personal communication) testing the accuracy of the probe on V-2 carcinoma in the rabbit eye found that it was necessary for the probe to come at least within two mm. of the lesions before a reasonable uptake could be achieved with the instrument.

It would be possible to increase the accuracy of this instrument by detaching the recti muscles or by inserting a small bulb on the tip of the probe to follow its path to the tumor side. These methods are being studied by other workers in the field at this time.²⁰

It is obvious when performing tests on posterior pole lesions that there is a marked difference in counts per minute when the counter is placed on the conjunctiva and when it is placed on the sclera. The differ-

ence in count usually amounts to a total of 60 to 70 units in a one-minute period. The total count is approximately 300 so that the percentage of conjunctival uptake alone is roughly 30 to 35 percent over that of the sclera. This has recently been noted by other investigators who feel that this factor may affect the accuracy of the test. We do not feel that this difference in the total amount of conjunctival uptake affects the result in any way since in the final analysis the total number of counts picked up by the conjunctiva cancels out on both sides of the equation. We have not had enough experience as yet with adnexal lesions to formulate any decisive report. This must be left for further study.

DISCUSSION

Since the last report presented at the Wills Hospital in 1957, the accuracy of the test has remained exactly the same, and the percentage of differences in all cases (both false positives and false negatives) has also remained exactly the same despite the additional number of cases studied. This may be coincidental, but more likely it denotes the over-all reliability of the test.

The test is unreliable in postoperative cases. It cannot be performed until at least six weeks have elapsed following surgery. The same holds for eyes recently traumatized by injury, prolonged transillumination or gonioscopy.

The radioactive phosphorus tests should not be performed on pregnant women or young children since radioactive material has a predisposition for fetal tissues. There are very few lesions in children for which radioactive phosphorus tests would be of value. Retinoblastomas do not show a significant uptake of radioactive phosphorus.

It is not necessary to repeat here the deficiencies of the P^{32} test which have already been well documented by other authors.^{14, 19, 21} The basic defects of the test have been well known and understood since its origination.

Despite its limitations, it is felt that the

TABLE 7
IRIS LESIONS
(33 cases)

Type	Number	P^{32}	Pathology
Malignant melanoma*	11	Positive	Malignant melanoma
Iris cysts	7	Negative	Iris cyst
Nevi	7	Negative	No reports

* 8 additional positive results without pathologic confirmation are not included.

test when properly performed is of sufficient clinical value to be used in cases of suspected malignancy. It is not intended to replace clinical judgment, interpretation, or experience. This was not the intent of the originators of the test. It should be considered a laboratory adjunct, just as other clinical

tests, for example, electrocardiograms and electroretinograms. The test will continue to be modified by ourselves and others until full knowledge of its advantages and limitations in each special area will be well known.

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THE MIGRAINOUS SCOTOMA AS STUDIED IN 618 PERSONS

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For years, at the Mayo Clinic, I spent some of my spare time quizzing hundreds of migrainous persons about their scotomas, trying to get answers to a number of the questions in my mind—such as:

What exactly is a migrainous scotoma?

What percentage of migrainous men and women have scotomas?

How often do migrainous persons have scotomas without a headache?

Does the fact that a person once had a typical scintillating scotoma prove that he or she is migrainous?

Are all transient scotomas migrainous in nature?

Can a scotoma be epileptic in origin, and, if so, what are its characteristics?

Are the bizarre and atypical scotomas of elderly persons sometimes due to little strokes?

I have been much impressed with the need for writing about the migrainous scotoma because scores of patients, much alarmed by their experience with this phenomenon, keep telling me that they described it to a half-dozen physicians without finding one who had any idea as to what it was.

Anyone who will read this paper will see that there still are a number of questions about transient and recurrent scotomas which need definite answers.

EARLY DESCRIPTIONS OF SCOTOMAS

The earliest description I have found of migraine with a scotoma is in the Deluge literature, written in Sumeria some 3,000 years before Christ. In the epic poem about Enke and Ninhursag, the ancient writer, speaking of the "Land of Dilmun"—possibly a sort of Eden—said that there

The sick eyed says not
"I am sick eyed"
The sick-headed (says) not
"I am sick-headed."

One can easily imagine the migrainous poet looking forward to a time when he will no longer have to suffer from his blinding headaches. Sigerist found another ancient Mesopotamian who spoke of times when

The head throbs,
When pain smites the eyes
And vision is dimmed.

This certainly is a perfect description of migraine.

Soranus of Ephesus (125 A.D.) described perfectly the "sudden darkening and blotting out of the vision, with dizziness. . . . They see before their eyes sparks like the flashes that come from spots on shining marble. . . . The head and eyes feel weighted down." Typical of migraine are such statements as that the distress is aggravated if the patient "gazes at a rotating potter's wheel," or looks at the glints of the sun shining on a river, or bends over forward. A good way of telling whether or not a headache is going to be migrainous is to sit with the head down below the knees. If the head starts to throb, it is a migraine, all right. Soranus noted also that the headache involves half the head, the backs of the eyes, and the *rucha*. "It dims the vision, and causes nausea and the vomiting of bile. . . . There is an aversion to food."

Aretaeus also described perfectly the pain in the eyes, or in the right or left side of the head, plus a desire to flee the light, and to get the soothing effect of darkness. He spoke also of a distortion of the face, with nausea, vomiting, sweating, and an aversion to smells.

A splendid article on migraine is by C. H. Parry who, in 1778, described his scotomas, which are exactly like those I see today. "It seemed as if something brown and more or less opaque was interposed between my eyes and an object, so that I saw indistinctly or sometimes not at all. . . . If I wished to see

anything I was obliged to look on one side. After it had continued for a few moments the upper or lower edge—I think always the upper—appeared bounded by an edging of light of a zigzag shape and coruscating nearly at right angles to its length." In Parry's case, as in the cases of thousands of men today, the phenomenon was never followed by a headache.

Dr. Edward Liveing in his splendid book, *On Megrim and Sick Headache* (1873), republished colored pictures of scotomas, taken from an article by Hubert Airy, the astronomer. Other fine pictures of scotomas are to be found in Gowers' Bowman Lecture, for 1895. Gowers got them from an artist who drew a bookful of them as he watched the phenomenon with his own eyes. More such pictures are to be found in F. Jolly's (1902) long and excellent article—one of the best ever written. Like me, Jolly was able to study the disease in himself. He had vision only in one eye, the other having been destroyed when he was nine. Curiously, he once observed a rare scotoma in reverse, with the line beginning at the edge of the field and then decreasing in size.

FREQUENCY OF A SCOTOMA AMONG THE MIGRAINOUS

Years ago, when I began this study, I soon found that many of my patients with definite migraine had never seen the phenomenon. Among 183 men whom I questioned carefully, 53 percent described what I thought was a scotoma, and among 435 women, 36 percent described it. Some writers have reported that about a third of their migrainous patients saw a scotoma. Dr. William Allan (1932) found a scintillating scotoma described by 60 percent of 122 men patients and 45 percent of 280 women patients. I do not remember anyone who ever noted that men are more likely than are women to see the bright zigzag line. When men describe a scotoma, there is seldom doubt about it because usually they have seen the line. Women are much more likely to de-

scribe vague spells of hazy vision plus bright spots of light.

Often it takes skill to get the story of a scotoma, and one must keep cross-questioning the person and going into details. It is, I think, diagnostic of migraine when a spell of poor vision lasts 20 or 25 minutes. As Gowers used to say, a visual storm that lasts only a few seconds is more likely to be epileptic in nature.

Atypical scotomas. As I talked to hundreds of migrainous patients, I learned of atypical scotomas. I am not sure that all these are bright or black spots or flashes of light or bright "balloons" or "bubbles" or stars or colored spots that come before or during the atypical headache are migrainous, but I suspect they are. I doubt if such visual storms come with ordinary headaches, but I did keep notes on this point. If I were making this study over again, I would accept as migrainous more of the vague scotomas some people describe, and this would raise the figures for percentage incidences in men and particularly women.

One man and one woman who described a typical scotoma with a zigzag line said it came *with* their headache. Three women said they had fuzzy vision *during* a headache and another spoke of "darkness" *during* a headache. An intelligent man said he sometimes saw "bursting bombs" when the pain in his head was at its worst. I see no reason why, with all stages of the migrainous storm in the visual center, a person should not see bright lights. I see no reason, also, why sometimes the scotoma and the headache should not be simultaneous.

My scotomas. In my own case, for a while I will wonder what has gone wrong with my vision. My sight will be a bit fuzzy as I could not focus my eyes sharply. Usually after a minute or two, on closing my eyes I will see a bright dot. Rarely I will have to wait five minutes before I can be sure of this. Soon the dot will extend into a luminous zigzag line which runs almost always vertically. A few persons tell me that in the

It runs horizontally. On one occasion mine started horizontally but it soon became erect and then bowed out to one side as it always does. Another time I saw a fine zigzag line running up and down and a coarse line running below it, horizontally. Later, the two lines ran together, end to end, and bowed out at last to the right. The line resembles a snake with its head erect, or an old-style fortification with projecting angles. In some spells the line is so brilliant one can see it easily with the eyes closed. It is claimed that the first man to call attention to this "scintillating scotoma" was M. Dianou. His Paris Thesis (1875) was called, "Du scotome scintillant."

The line pulsates rapidly as if it were a rubber tube through which some fluid was being pumped with rapid impulses. The whole line will also rotate a bit on its axis, making it will move up and down a little. The rate of pulsation is so fast I have never been able to count it, but I think it is around 180 beats a minute. In 1835, Serre d'Alais, in an excellent description of his own scotomas, said that the pulsation was between 190 and 200 throbs a minute.

Some persons, in occasional spells, will see rainbow colors, usually or perhaps always, on the inner side of the zigzag line. Occasionally, I have seen such colors, usually purple and yellow. D'Alais saw green, yellow and blue. Sometimes I see a black zigzag line which, strange to say, is luminous. It lies alongside of the white line. I wondered if the presence of these colors can help us determine the location of the storm in the brain or the retina.

As minutes pass, the line keeps bowing out more and more widely toward one or other side until it seems to disappear beyond the edge of the field of vision. With this, the usual acuity of vision returns to normal. I have experienced dozens of my scotomas and they lasted from 20 to 28 minutes. Most of my patients are sure that scotomas last 20-25 minutes, but one occasional man or woman said it lasted only 10 minutes.

Some scotomas do not interfere much with

reading. During the part of my spell in which the zigzag line is brightest, I usually have trouble reading, but in many spells I can easily keep at my work. In occasional spells I marvel because my vision is so little disturbed. My central vision always remains good, so that I can always read if I have to. As Parry said, one can always "look around the blind spot."

How definite is the blindspot? A few cases are on record in which a migrainous blind-spot was mapped with a perimeter, but mine are too indefinite for that. Chambers (1926) could not map scotomas which left the person's vision only a bit hazy. If, during a spell, I look at a sheet of paper or the sky with either one eye or both eyes, I cannot recognize any blank areas, and if I look at a picture I do not have a feeling, as some few migrainous persons do, that parts of it are lacking. However, while trying to read, I often note that I am seeing only certain letters or words or parts of words. In my case the scotoma usually is perceived equally by both eyes, which of course indicates that the storm is in the brain.

Hemianopsia. Three of my men patients described a hemianopsia with zigzags, and three more described a hemianopsia alone. One of them called his trouble a "black-out on one side," and another said he recognized a hemianopsia in only some of his spells. Three of my women patients had a hemianopsia with zigzags, and one once had a hemianopsia without zigzags. One described a black-out of the upper half of her field of vision, such as has been described by Galewowski and others. One of my women patients said, "If I look down, I may see my hand but not my arm."

Once, when I had a scotoma as I was driving my car along a narrow country road, I must have had a left hemianopsia because suddenly I discovered a car a few yards away, bearing down on me. I had not seen it as it approached. It is curious that just before this happened I was not conscious of this decided defect in the left half of my field

of vision! Several of my patients, after having had a similar experience while driving, decided that always, when they got a scotoma, they would stop a while and wait for the return of their vision.

Bowing to right or left of the zigzag line. In some of my spells the zigzag line bows out to the right and in some it goes to the left. This year the succession has been: R.R.L.L.R.L.R.R.L.L.R.R.L.L.R.L.L.R.L.R. Some persons say that their zigzag always bows to one side. According to some writers, a bowing of the line to one side means that the headache will be on the other side, but I haven't data on this point.

Time of day when scotomas come. Many persons have spoken of the curious periodicity with which their scotomas come, perhaps waking them, usually at a certain time, such as 4:00 A.M. My own experience is that in the last 10 years, since I have kept records of my spells, I have found that most have come between 11:00 A.M. and 1:00 P.M. They are a little more likely to come if I have had insomnia, but many a bad night's sleep does not bring a scotoma, and many a scotoma comes when I can see no explanation for it. The coming of many scotomas about 11:30 A.M. suggests that the "storm" comes with some tide in my metabolism. A similar phenomenon, noted in many cases of epilepsy, is well discussed by Franz Halberg (1953). The same metabolic tide may account for the hunger pain which used to hit me about 11:30 A.M., even when I had no ulcer and had not eaten breakfast.

Details on the timing during the day of my scotomas. In the years from January 1, 1950, to December 31, 1957, I had 107 scotomas, 69 of which came in the three hours from 10:00 A.M. to 1:00 P.M. There were 17 in the hour from 10 to 11; 25 in the hour from 11 to 12, and 27 in the hour from 12 to 1. One spell came at 8:00 A.M.; there were from four to six in each of the four hours between 2:00 and 6:00 P.M.; there were three in the hour after 7:00 P.M.; two in the hour after 8:00 P.M. and one right after 10:00 P.M.

On six occasions in six years I have had two scotomas in one day—for no reason that I could see. Once the two scotomas came at 10:15 A.M. and 11:40 A.M., and another time they came exactly two hours apart. In each case, the second time, the zigzag line bowed in a direction opposite to that in the first scotoma.

Recently, I had the unique experience of getting a second scotoma 10 minutes after one had disappeared to the left. The second one started in an unusual way in that a short zigzag line appeared well out in the left half of the field and quickly moved out near the edge. There it remained for 12 minutes and then disappeared. This is of interest if only because it contradicts the belief of some men that for some time after the migrainous trap has been sprung, it cannot be sprung again.

The sequence of scotomas during one year. An example of the sequence of my scotomas in one year, 1958, is as follows: February 9th twice; February 12th twice. About this time I had a trace of fever due to a thrombus in my left saphenous vein. I then went free until May 26th and 28th. Then came spells on July 11th, August 24th, October 20th, October 26th, November 19th and 23rd, and December 26th. Usually I could not guess why a scotoma came. Often when I had days of heavy strain and much fatigue I had no scotoma. The earliest scotoma I can remember came when I was in college.

Atypical scotomas, probably migrainous in nature. I have seen a few peculiar scotomas which seemed to me to be variants of my migrainous one. I think they are worth noting because some day they and other atypical ones may help to throw light on the mechanism that produces them. Once, after five minutes of seeing only a luminous cloud, I saw a chain of bright rods which soon fused into the usual zigzag line. In an unusual spell, a part of the zigzag line broke up into fragments. Another time there was a strange finish to the scotoma, with a grid of bright spots which enlarged to circles, and later changed to fine luminous lines. On one occa-

sion a brown luminous grating filled the space within the bowed zigzag line. This grating remained bright for 30 minutes after my vision had cleared.

In a unique spell I saw a duplication of the zigzag line into three or four lines, suggesting parallel combers running up a beach. Rarely, I have seen zigzags which did not pulsate.

With some of my scotomas visual fuzziness lasted only 10 minutes, while in four spells I had no fuzziness at all, and could read comfortably throughout the 20 minutes during which I could see the bright zigzag line. Once I saw a small barely visible zigzag line which did not enlarge and develop as usual. In another queer short spell I saw a typical bright spot with only my left eye. This disappeared in a few minutes and after that I had a slight fuzziness of vision, plus a large, slightly luminous area in the lower half of my combined field. I probably had a spasm in one of the upper retinal arteries.

Three persons with unusual scotomas. A woman who, in her severe attacks of migraine would stagger if she walked, told me that at times she had a rare type of scotoma in which, while her vision was fuzzy, she saw double. She never saw a zigzag line. A physician told me that at times he saw a brilliant light which started in a small area and then spread all over his field of vision. It got brighter and brighter and then faded. There was no zigzag line, no nausea and no headache. A woman said that once she kept seeing a zigzag line all through one night.

Immanuel Kant's scotomas. Dr. Richard D. Loewenberg (1953) called my attention to Immanuel Kant's description of his scotomas in his postscript to *The Art of Prolonging the Human Life*. For years Kant had been blind in his left eye. Several times a year, as he was reading, the letters would become "confused and mixed, with a . . . brightness to the point of . . . illegibility." This lasted less than six minutes. Then he saw the zigzag bright line. He concluded that the cause was in the brain, because the image did not move with the movements of his eyeballs.

My attempts to abort my scotomas. If, the moment I see that a scotoma is starting, I close my eyes and keep them closed, the bright spot may almost disappear; and for five or 10 minutes I will hope that I have blocked the thing. But then the zigzag line will develop rapidly in all its brightness, and I'll have a scotoma peculiar only in that the phenomenon is so speeded-up that all of it takes place in 10 or 15 minutes. This observation, many times repeated, shows that the mechanism can be modified, probably by the amount of light entering the eyes.

Once I saw a brilliant line which almost certainly was the beginning of a zigzag. I closed my eyes and it rapidly faded and disappeared, which suggests that, in rare cases, one can abort a scotoma.

Some migrainous women who commonly get severe sick headaches tell me that often they can get by with a mild headache if, the minute the scotoma starts, they quit work, and lie down in a darkened room. Some go completely free of headache if, with the scotoma, they can only fall asleep. Perhaps the lack of light shining into the eyes causes the visual cortex to become less sensitive.

Do a few scotomas seen in a lifetime mean that the person is migrainous? My impression is that if a person has seen only once or twice in his life a typical scotoma, we can assume that he has inherited a gene for migraine. Then, if in his later years he has curious transitory spells, perhaps of nausea or dizziness or numbness we can be the surer that they represent variants of migraine.

A difference in the incidence of "headacheless" scotomas in men and women. In my series of 618 cases, 12 percent of the men and 0.7 percent of the women told of having had scotomas without ever a headache. It is curious that the migrainous men, who usually have only a mild headache, or none at all, are the ones most likely to have a brilliant and typical zigzag scotoma. Professional men with migraine, when interviewed, usually said they had had only scotomas. Thus, 38 of 44 migrainous physicians whom I once,

at a convention, questioned on this point said they had had many "solitary scotomas" with never a headache.

Six of the men and four of the women in my series of 618 persons said that in all their days they had experienced only one scotoma, but that was vivid and typical. One man, an eminent physicist, in his 47 years, has seen two typical scotomas. An able woman, aged 45 years, with a history of many sick headaches, also can remember only two "blind spells." Some women can remember having had up to a half-dozen scotomas.

One woman who had had only one scotoma in her lifetime told me this had come when she took the dye for a roentgenologic study of her gallbladder! This observation could be used as a starting-point for some research. Some of Dr. Meduna's patients, while breathing 30-percent carbon dioxide gas, saw a scotoma with elaborate figures that sometimes gyrated. As I will note later, migrainous aviators being studied in a decompression tank will often get a scotoma.

Scotomas with marked blindness. An able woman who had had only two scotomas and a few sick headaches in her life, assured me that with one of the spells she had gone "completely blind," and in the other had become "so blind she had to grope about." Her sister was highly migrainous. Chambers (1926) described such a case in which the woman, when in a scotoma, was so blind she could count fingers at only two feet. A little further on I will describe migraine with marked blindness in one eye but not in the other.

The whole brain is disturbed with a scotoma. Many persons report that their brain does not work well when a scotoma is present. Often, when fuzzy-eyed and unable to read comfortably, I have employed my time writing a family letter, long-hand. Later, on checking the letter, I have found several mistakes; I had written words other than the ones I had thought I was writing. Several persons have told me of similar happenings, and several women and a male physician have

told me of a mild aphasia that came when they tried to talk during a scotoma.

The literature is full of accounts of these bodily disturbances that come often during a scotoma—which show that the storm can be widespread through the brain. Gowers described persons who, with their scotomas, had a numbness that would spread up one arm from the hand, or who felt a numbness across their lips, or who were temporarily aphasic, or who felt pins and needles in both hands and both lips or the tongue. French authors have often described the numbness, and I have seen several persons who complained of it.

Some of my patients will not drive a car while they are having a scotoma, not because of defective vision, but because they know that, in the spells, their judgment is impaired, so that they cannot estimate distances or speeds as well as they ordinarily do.

More evidence of a storm widespread through the brain during a scotoma was the "twitching of one eye," experienced by a patient of mine—a man who saw "colored spots" before a headache. A woman I know, with a severe type of migraine, for an hour or two before a headache, is distressed by a feeling of pulsation in one cheek. One of my patients, when her vision is fuzzy, staggers if she tries to walk.

A woman I know yawns for a while before a scotoma starts, and then her eyes water. A physician, with his scotomas, gets an anesthesia and numbness in his tongue and in the index and middle fingers of his left hand. Some persons get unusually hungry, or they urinate much just before a scotoma comes. Jules Raullet (1883) mentioned persons who, with a scotoma, felt ants crawling up an arm, or who got a temporary weakness of an arm, or a slight aphasia, or a precordial distress, or swelling of the lips. A woman patient of mine, during her headacheless scotomas, gets pain in the right upper quadrant of her abdomen.

Sensitiveness to light after a scotoma. The retina or the visual center can be abnormally

sensitive for a while after a scotoma, and many migrainous persons, during an attack or after it, feel more comfortable in a darkened room. One of my patients who gets a hemianopsia with his migraine has trouble with overly sensitive eyes for five hours afterward.

One Sunday morning I had a brilliant scotoma. That afternoon, at a musical recital, I was distressed by a brilliant after-image of the piano which I got if I looked at it for more than a few seconds. Evidently my retina or my brain was tremendously hypersensitive. A few weeks later, when in the same hall and in the same seat, I again listened to a recital, I could look at the piano for minutes at a time without getting any after-image. Recently, without having had a scotoma, I got such brilliant after-images of my television screen that I could not watch the picture. Evidently, the eyes or brain can become tremendously sensitive to light in the absence of a migraine.

Other after-effects of a scotoma. Sometimes after a scotoma I feel a bit depressed or toxic or tired; but, as I have said, I practically never have a headache. Usually, as soon as the zigzag line disappears, my eyes are again able to work comfortably. But, occasionally, a little fuzziness of vision remains, and for a half-hour or more, if I close my eyes, I can see a faint luminous cloud on the side of the field where the zigzag line was.

WHERE DOES THE STORM OF A SCOTOMA ORIGINATE?

It is usually assumed that the scotoma of migraine arises in the visual centers of the brain, and this is highly probable for several reasons. During a scotoma, the symptoms that often appear in several parts of the body could arise only in the brain. There are other reasons, of course, for locating the disturbance in the brain—facts such as that usually both eyes are equally involved, that the blindspots are vague, and that central vision is retained.

The movement of the zigzag line on moving the eyes. What has puzzled me is the fact that when I and some of my patients experience a scotoma we can throw the zigzag figure to the left or right or up or down by appropriate movements of the eyes. Dr. Peliffe (1917, p. 141) spoke of "a slight cloudy spot which seems to follow the eye in reading." At first glance, this movement indicates that the scotoma is formed in the retinas but, as Dr. Wilbur Rucker of the Mayo Clinic tells me, the explanation can well be that for a lifetime we human beings have been accustomed to seeing an image move with the movement of our eyes. Against this idea is the fact that when I have tiny brilliant and momentary scotomas of a type which, I suspect, are due to a thrombosis or momentary spasm in an arteriole in my visual center, I cannot move them about by moving my eyes.

Dr. George M. Gould thought the storm started in the cortex but he quoted Brewster as saying they were produced in the retinas. H. Klein (quoted by Keller, 1920) thought the retinas are involved. Other men have located the "storm" in the optic nerves, the chiasm, the optic tracts, the geniculate bodies, or the cortex. Jolly put it in the corpus geniculatus externum. Galezowski (1878) thought it should be in vasomotor fibers connected with the Vth pair of nerves; perhaps also in vasomotor nerves in the retinas. Ludwig Manthier (1881) thought the storm came in both brain and retina. He wrote that when the retina is acting abnormally, one cannot produce a sensation of light by pressing on the eyeball. Chambers (1926), A. M. Cahan, quoted by Schumacher and Wolff (1941), G. Bonamour (1952), Duke-Elder (1949, vol. 4), H. Richter (1935) and Keller (1920) all placed the source of the scotoma in the cortex.

Dr. Harold Wolff once wrote me that his impression was that scotomas might originate either in the cortex or the retina. Dr. Wilder Penfield wrote that his experiences during operations on the brains of unanesthetized

patients have indicated that scotomas can arise in the cortex. In 1947, Ostfeld and Wolff concluded that "simple somber-hued scotomas may originate in the retina or prechiasmatic optic nerves, and that the more elaborately structured and brightly colored visual disturbances arise in the occipital and adjacent portions of the hemisphere." They described scotomas that were produced by vertebral angiography. Schumacher and Wolff (1941) and others have assumed that the scotomas start usually with a constriction of arteries in the brain.

The evidence obtained from electroencephalograms. Evidence in regard to the site of the physiologic disturbance which produces a scotoma has been reported by a few men who made electroencephalograms of a few patients while they were going into a spell of migraine. Small abnormalities were found in the records made in the occipital regions. Such observations were made by Engel, Webb, Ferris, Romano, Ryder and Blankenhorn (1944) (see also Ramano, Engel, Ferris, Ryder and Blankenhorn, 1944) when they recorded EEG's from a number of (usually migrainous) men who got a scotoma as they were being decompressed after a simulated flight to an altitude of 38,000 feet. In two out of 17 cases the investigators found a focus of delta waves and irregularity in the record made from an occipital lobe. However, their graphs, as published, do not show much change from normal.

In the discussion, Dr. Harold M. Somberg said he had seen aviators with similarly produced scotomas, but he had not seen any significant change in the encephalograms. Also, in the discussion, Frederic Gibbs reported that he had obtained encephalograms on many persons during a scintillating scotoma, and had not seen any changes in the records. Bickford and Peters (1953) at Mayo's, reported having seen little to talk about in records of 100 migrainous persons. J. Krischek (1956) saw little difference when he compared encephalograms made during a spell of migraine with those made during a free interval.

My own encephalograms made once as I was finishing a scotoma were essentially normal.

Bang, Dalsgaard-Nielson and Hertz (1951) saw no dysrhythmia in encephalograms made in the vasodilator stage of migraine. When in a few cases they saw a dysrhythmia brought out by the giving of drugs, they felt the change must have been effected by vasospasm in the brain. W. Bärtschi-Rochaix (1954) also spoke of small abnormalities in the encephalograms due apparently to circulatory changes in the cortex. Like Gowers, he realized the great importance in such studies of recognizing migrainous persons suffering from a concomitant epilepsy. The investigator must never use for such studies patients with epilepsy or psychosis or a tendency to great violence in either them or members of their family. Robert Cohn (1949) studied encephalograms made during scotomas, but it is not certain that he took sufficient care to rule out carriers of epilepsy.

Scotomas in persons without retinas. Hoping to get a definite answer to the question of the point of origin of scotomas, I have for long looked for a blind person with both retinas destroyed but still suffering from migraine with scintillating scotomas. I have found nothing definite in the literature. Raullet (1883, case 23) described a woman 28 years of age who, for 10 years, had suffered from terrible "menstrual headaches" preceded by weird lights and sometimes a hemianopsia—probably migrainous. Then, although tabes dorsalis had produced in her a bilateral optic atrophy, her scotomas persisted. This suggested that they were being formed in the brain. Unfortunately, Raullet did not say that the persisting visual storms were the same as they were before blindness came, or that they still were part of a migrainous spell. Galezowski records cases of scintillating scotomas seen by an eye in which there was either an atrophic choroiditis or white atrophy of the papilla, or a syphilitic destruction of the retina.

My search for retinaless persons with still

a scotoma. In my search for a retinaless person still having migrainous attacks preceded by a scintillating scotoma, I was helped by my blind patient, Mrs. Edna Sollars, who, at the age of 20 years, had both eyes enucleated because of a painful blindness, probably due to an acute glaucoma. Shortly after the operation, she began to have severe migrainous headaches—which kept coming for the next 50 years. She still has a scintillating scotoma but it is atypical in that it lacks the zigzag line. Shortly after the enucleation, she suffered much from "terrible glares of light, white and colored, with a constant 'streaming' of bright spots." After two months of this, there came the type of scotoma which she still has. With this, she sees "a dark egg-shaped area with, in its center, two shining dots, one white and one black. Around the edges of the egg is an irregular black border, which fades away to nothingness at the top." At the base is a "sand dune with many brilliant grains of sand in constant motion." There are also streaks of light darting about rapidly. Mrs. Sollars' experience shows that a migrainous type of scotoma can be formed in the absence of eyes.

Incidentally, as Mrs. Sollars was corresponding with most of the American Schools and Workshops for the blind, she received letters from 37 officials who said they knew of almost no migraine in their total of 2,623 blind children and 633 blind adults. This suggests that seldom will a migrainous spell arise in an inactive visual center.

The only official who reported a number of almost blind persons with migraine was Mr. George A. Brown, of Los Angeles, who can recognize migraine in his 140 blind workers because he suffers from it himself. I interviewed 12 of the migrainous employees in his plant and found two with a condition that strongly suggested that the scotomatous "storm" was arising in the brain. A woman aged 50 years, a diabetic, almost totally blind, was still having migrainous spells with a zigzag scotoma. Since her corneas and lenses and media were clear, the inference was that

her retinas had been almost completely destroyed by a diabetic retinitis. Unfortunately, I could not check this as I had forgotten to take an ophthalmoscope with me.

Suggestive, also, of a cerebral origin of a scotoma was the case of a man 55 years of age who, three years before I saw him, was suddenly felled to the ground by a "stroke." He quickly recovered from this, but promptly lost all vision in the left eye. A day or two later he lost almost all of the vision in the right eye. He could see fingers only on the outer edge of the field. He then began to have sick headaches with a scotoma with a zigzag line. These two cases certainly suggest that the scotomas were coming, not from small remnants of the retinas, but from the brain.

Vasoconstriction during a scotoma. For years investigators have reported seeing, during a scotoma, vasoconstriction in the retinal and conjunctival arterioles. Much of this work has been done by Dr. Harold Wolff and his associates. Schumacher and Wolff (1941) and Wolff (1950) found usually vasoconstriction at the beginning of an attack of migraine (see Wolff's summary of his work in *Migraine and Vascular Allergy*, 1956). Ostfeld and Wolff (1947) were able to produce vasoconstriction with scotomas by injecting levarteronol intravenously. They observed scotomas produced by vertebral artery angiography, also by pressure on the eyeballs sufficient to produce retinal ischemia.

Ostfeld and Wolff found vasoconstriction in the conjunctival arterioles in the early stages of migraine, as did Wolff, Ostfeld, Reis and Goodell. Ostfeld and Wolff thought that at the start of an attack there was probably vasoconstriction either in the retina, the retinal artery or the occipital hemisphere. Chambers (1926) usually saw vasoconstriction in the retinas of persons with a scotoma, as did Remky (1953), but Foerster failed to see vasoconstriction during attacks of migraine, and Schultze (1922) seldom saw much change. Harold M. Somberg (in the discussion of a paper by Ramano, Engel, Ferris, Wolff, Ryder and Blankenhorn) said

chomotor type of activity in the left antero-temporal area and a seizure type in the right anterotemporal area. Unfortunately, Dilantin did not help the woman.

Can a scotoma be purely epileptic in origin or is it always due to a mixture of migraine and epilepsy? I have wondered if a few atypical scotomas might be due purely to epilepsy, and according to Gowers, they can be, but he maintained that they are different from the scotomas of migraine. They differ in that they are momentary, and with them, the person may see figures and faces and scenes. Persons with pure migraine do not see such things. Gowers doubted if a lateral hemianopsia is ever seen in epilepsy, but he had epileptic patients with a brief transverse hemianopsia. He said that vomiting can follow a mild questionable spell of epilepsy, but severe headache never follows such a spell. Also, when vomiting follows an epileptic scotoma, it comes right away and not late, as it does in many cases of migraine. Duke-Elder wrote of scotomas in epileptics.

Gowers and others have seen cases like those described by Liveing in 1873, in which migraine alternated with epilepsy. But Gowers was satisfied that in such cases one is dealing with migraine plus epilepsy. He saw that since the two diseases are so common, they must, every so often, appear together in a patient. When faced with a severe or atypical form of migraine the physician must always inquire if there are any epileptics among the patient's relatives. Gowers had noted, also, what is so essential, that while inquiring into the family history, one must ask, not only about people with fits, but also about violent people, alcoholics, and mentally disturbed, mentally retarded, or delinquent people.

PECULIAR SCOTOMAS OF LATER LIFE

Many persons have their scotomas mainly late in life. Most of mine have come since I was 60 years of age. Many migrainous persons wind up in their later years with their headaches and nausea gone, and only sco-

tomas left. A patient of mine—a woman aged 40 years—who used to have sick headaches, now gets the zigzag scotoma with nausea, but no headache. Another woman, when under strain, gets a scotoma, and vomits for days, but hasn't a headache. A middle-aged woman occasionally "goes blind" but she gets no headache.

I have had rare scotomas since I was in my teens, but practically never one with a headache until I was 67 years of age, and then the ache was mild. I now have spells of a burning distress in my right temple but this does not follow a scotoma, and it is not associated with nausea or any other symptom of migraine except a mild depression.

A curious story was told me by a man who, in his boyhood, had sick headaches and scotomas with the zigzag line. At the age of 40 years he was still having an occasional throbbing unilateral headache, sometimes preceded by a scotoma with fuzziness of vision but he had lost the zigzag line.

Scotomas due perhaps to cerebral arteriosclerosis with little strokes. I know a number of elderly persons who have seen a few bizarre scotomas suggestive of a thrombosis in a tiny artery in the visual center. These persons had been having what I call little strokes.

As I said above, the literature contains many reports of a migrainous vasoconstriction that lasted until thrombosis took place in an artery. Dr. J. P. Murphy (1955) described a case in which a woman's scotoma one day ushered in a stroke with a hemiplegia. Gowers (p. 86) described the case of an elderly woman who one day, during a sick headache, had a little stroke, with a hemiplegia and an aphasia that lasted a week. Gowers spoke also of "senile epilepsy" ushered in by an aura of migraine. He described the case of a man with zigzag scotomas plus a hemianopsia, usually lateral, but sometimes transverse, plus a vertical diplopia. Following a scotoma, the man sometimes had an attack of grand mal.

Migrainelike "storms" have been de-

scribed to me by a few elderly persons who did not appear to be migrainous, and, so far as I could learn, never before had had any sign of migraine. In such cases, I suspected that the scotomas were caused by vascular changes in the brain, similar to those which, on rare occasions, will produce a spell of grand mal in an elderly man who never was epileptic and who has a normal electroencephalogram. Sir Stewart Duke-Elder (1949) once described a case of malignant hypertension in which the patient had "migrainous hallucinations" with hemianopsia and epileptiform attacks—all of which cleared up after a lumbar sympathectomy. Brain (1947) and Zentmayer (1912) described such cases, and I have seen several.

One of my most interesting cases of atypical migraine is that of a woman aged 44 years, who did not look migrainous, who had no known case of migraine in her family, and who had never had a sick headache. Shortly before I saw her, she had begun to have little strokes. Following one of them, she began to have typical migrainous headaches, some with a scotoma and some without. They were relieved with the help of Gynergen. A while later, after another little stroke, which may have destroyed some bit of brain necessary to the production of sick headaches, the woman lost her migraines—scotomas and all. I know a man, long, a sufferer from scotomas, who lost them after a stroke. These stories remind me of good-natured men I have known who, after a stroke, became unpleasant, irascible and unreasonable. After another stroke they got back their old good nature and kindness!

A big stout widow, aged 59 years, who did not look migrainous and never had had a headache, was wonderfully well until the age of 57 years, when she was badly shaken up by a little stroke. A year later she had another spell in which she thought she was having a stroke. It ended with what looked like a typical severe migrainous headache. With this she kept seeing flashes of light,

and all night she kept having severe pain in her head. Later, she had another attack of what looked like migraine and following this she had no more trouble. A year later when I last saw her, she was well.

A usually healthy woman aged 73 years, who knew of no migraine in her family, and practically never had had a headache, one day thought she was having a little stroke. With this she experienced a brilliant scintillating scotoma, such as she had never seen before. Foerster once told of a man who, in his fifties, after little strokes, developed migraine.

My own scotomas of a type due probably to arterial spasm or thrombosis of a small artery in the brain. In my sixties I began to see a few unusual scotomas, so very different from my ordinary ones with the zigzag line that I felt they must have been produced by spasm in, or thrombosis of, a little artery in my brain. One day suddenly I saw a big splotch of red on an orange-tinted field. For a few minutes I had no central vision, and felt as if I had looked at the sun. There was no zigzag line. The color soon began to fade, and in 10 minutes the spot was gone, and my vision was normal. For the rest of the day I had a bilateral headache such as is very unusual for me.

On another occasion I woke about midnight with a weird visual storm. Brilliant purple colors were weaving in and out, as if on the top of some boiling liquid. For a moment, some yellow splotches appeared. The picture ended in a few minutes. One day I woke at 2:00 A.M. with a headache. At 8:00 A.M. I woke with another headache and in a few minutes my vision was in a strange turmoil. I seemed to be seeing a road cracking up with a severe earthquake. When I was 70 years of age, I woke after a good night's sleep with my retina remarkably hypersensitive. My photophobia lasted for hours.

A year later I had a very unusual spell that started in a moment with a marked impairment of vision. I saw a bright spot of

light, with a reddish cloud near it. This disappeared in 25 minutes. I much doubted if this scotoma was of migrainous origin. On another occasion a bright spot appeared; it quickly changed to a black spot and then this faded out. A little later, I saw a glowing ball of light, which disappeared in five minutes and was replaced by a faint zigzag line. After this faded, there remained for a while some hemianopsia.

Another time, when I was getting a thrombus in my left iliac vein, for a matter of seconds, I lost vision in the upper half of the field in my left eye, and in this area saw a brick red color. Evidently, there was a brief spasm in the left inferior retinal artery.

BRILLIANT SCOTOMAS IN CHILDHOOD

A woman once told me of brilliant colored scotomas which used to terrify her when she was a child. She had no headache with them but would vomit the next day, and hence the phenomenon was probably migrainous in nature. Confirmation of this diagnosis is to be found in the fact that at the age of 29 years, after a domestic tragedy, she began to have severe migrainous headaches which started with a typical scotoma.

A physician who, at the age of 46 years, was still having severe migraines, told me that as a child, lying in the dark, he would often see brilliant lights which probably were manifestations of migraine. So many persons have told me of these bright scotomas in childhood that I now suspect that the brilliant vision I saw at the age of four years was part of my life-long tendency to migraine. This vision was so striking that today, 70 years later, I can still see it faintly in my mind's eye. It looked like the ceiling of a Gothic chapel, painted a glowing light blue, and studded with big glittering stars. Mixed with this was the rigging of a sailing vessel! I suspect that at the time my brain was strongly stimulated by some virus infection. We need more information on these phe-

nomena, and pediatricians should study migraine in childhood.

SUMMARY

For years, with a note book in hand, I questioned migrainous persons about their scotomas. With records of the experiences of 618 such persons, I started writing. This article is needed if only because few physicians appear to be sufficiently well acquainted with the migrainous scotoma that they can recognize it when they hear about it.

There are good descriptions of scotomas in the ancient Sumerian literature; also in the writings of Soranus and Aetius. Also in the literature are excellent pictures of typical scintillating scotomas.

I found 53 percent of migrainous men have scotomas while only 36 percent of migrainous women have them. Men are much more likely to see the zigzag line while women are more likely to have atypical scotomas. Often it takes skill to get the story of a scotoma from a patient. Most of the atypical scotomas with only "bright stars" are probably migrainous. Diagnostic of migraine is the fact that a scotoma lasts about 20 minutes. The scotoma can appear before the headache or with it. My own scotomas are described. A bright spot comes; this forms a zigzag line that bows out to the right or the left, and in 20 minutes or so disappears over the edge of the field of vision. The line pulsates about 180 times a minute. The scotomas may be colored. Often there is a black zigzag line. Some scotomas greatly interfere with reading, while some interfere hardly at all. The person who wants to read can always "seem to look around the blindspot." The blindspots are usually too indefinite to be mapped with a perimeter.

A hemianopsia, when present, is often vague.

Most of my scotomas come between 11:00 A.M. and 1:00 P.M. They come at irregular intervals throughout the year. There may be none in two months, or two in a day. There is no clear explanation for this.

There are many atypical scotomas, probably migrainous in nature. The zigzag line will occasionally be duplicated. One patient with a scotoma saw double.

The fact that a person has seen only one or two scotomas in a lifetime is enough to show that he or she is migrainous. A history of having had scotomas is therefore very helpful in recognizing as migrainous some curious transient spells of nausea, dizziness or great fatigue.

In the present 618 cases, 12 percent of the men and 0.7 percent of the women had scotomas with never a headache. Thirty-eight out of 44 migrainous physicians, seen consecutively, had scotomas without a headache. Rarely, a person will go almost completely blind in a scotoma.

The whole brain is disturbed with a scotoma. There may be a slight aphasia, with numbnesses, formication, pins and needles here and there, a weakness of some muscles, frequency of urination or pain in the thorax or abdomen.

For hours after a scotoma, there may be great sensitiveness of the retina or the brain to light. The person may then see a faint luminous cloud.

It is not certain just where in the brain or the retina the storm of a scotoma begins but most men place it in the brain. Puzzling is the fact that moving the eyes can throw the scotoma from one side to the other. It is not quite adequate to place the center of the whole storm in the cortex, because there can be vasomotor changes in the eye, paralyses of external ocular muscles, sensory disturbances in the face, and nervous storms all over the body.

Electroencephalograms made while a patient is having a scintillating scotoma usually don't show anything abnormal. When they do, it may be that the patient is a carrier of epilepsy.

There are a few case records in the literature that suggest that a person with the retinas destroyed can still have a scintillating scotoma. I found two persons with a zigzag scotoma and probably no functioning retinas. Another patient, still getting migrainous scotomas at the age of 75 years, had her eyes enucleated at the age of 20 years.

Statistics show that the blind rarely suffer from migraine.

The term ophthalmic migraine is probably unnecessary. It may mean only a migraine in which the patient has scotomas. The term ophthalmoplegic migraine is also of doubtful value. In many of the reported cases the disease appears to have been migraine plus arteriosclerosis, psychosis, with hysteria, epilepsy, little strokes, a brain tumor, or a rupture of a tiny aneurysm. In some cases the story and findings suggest that a migrainous spasm in an artery of the eye lasted so long that a thrombosis resulted.

There are cases of migrainous transient blindness in one eye with good vision remaining in the other. The case of a patient with this type in whom there may have been an epileptic component is described.

When scotomas are due to epilepsy, they last only a few seconds and may be associated with visions of faces. These do not occur with pure migraine. When spells of migraine and epilepsy alternate, the patient probably has two diseases.

Migrainous scotomas tend to change in character as the person gets older. Some of the peculiar scotomas seen in later life are probably due purely to arteriosclerosis of the brain. Several such cases are described. Also, described are some of my own peculiar scotomas which were probably not migrainous but arteriosclerotic. Brilliant scotomas are seen by children.

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ANTIGENIC PROPERTIES OF FRESH AND STORED CORNEAL PROTEINS*

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Antigenic properties of corneal tissues have been studied by a number of workers and by a variety of techniques. Smith and Woodin (1953)¹ have demonstrated the presence of antigenic substances in whole bovine cornea by immunizing rabbits with bovine corneal extracts and testing the antigen-antibody systems present in the serum by gel diffusion techniques.

Klima (1950)² used an intracorneal technique to demonstrate antigenic reaction in the cornea. He showed that two injections of a corneal extract from one animal, given two weeks apart, gave rise to a reaction, but this seldom occurred if the two injections were from different donors.

Basu and Ormsby (1957)³ inserted donor cornea into the interlamellar space of rabbit's cornea and showed that when epithelium was removed from both homologous and heterologous grafts, the incidence and se-

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verity of reactions were reduced. They also showed that beef corneas were more antigenic when grafted into rabbits eyes than were lamb, monkey, duck, and chicken.⁴

Our work is a continuation of these studies,⁵ using immunologic tests.

METHODS AND MATERIALS

Extracts were made from: (1) Fresh whole rabbit cornea; (2) fresh bovine cornea—(a) whole, (b) mucoid fraction, (c) collagen fraction; (3) fresh bovine cornea without epithelium; (4) stored whole bovine cornea—(a) -79°C . for 60 days, and (b) $+4^{\circ}\text{C}$. for 30 days.

PREPARATION OF EXTRACTS

The whole eyes were removed immediately after death and were immersed in normal saline containing 500 mg. of streptomycin and 1000 units of penicillin per cc. After four washes in this solution (approximately 30 minutes), the corneas were excised from the globe, emulsified in a Waring Blendor and the proteins were extracted in sterile saline at 4°C . for three days. The corneal suspension was centrifuged each day, supernatant fluid removed, and sterile saline replaced. The pooled corneal extract was dialyzed against distilled water at 4°C . for 48 hours and then concentrated in a dry freezing apparatus. The solid portion was redissolved in sterile saline and the total protein estimated by the micro-Kjeldahl method, and made up to the required strength. The residue from the original saline extraction was used for the preparation of mucoids following the procedure described by Woodin (1952).⁶ This residue was used for the extraction of collagen according to the technique of Krause (1932).⁸

PREPARATION OF ANTISERA

Antisera were prepared by immunizing rabbits with the above extracts. A sample of blood was taken from each rabbit before the initial injection of antigen. The rabbits were then given twice-weekly intravenous injections of the appropriate antigen (containing approximately one percent total proteins) in

series of 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, and 2.0 cc. This latter dose was given twice weekly from the seventh to the 12th week. Blood was taken from rabbits by heart puncture after four, eight, and 12 weeks, and the sera were preserved with 0.01 percent merthiolate and stored in a deep freeze at -30°C .

GEL DIFFUSION TECHNIQUE

Our technique was a slight modification of the method of Bowen (1952).⁷ A stock solution of 0.8- and 1.6-percent filtered agar containing merthiolate (0.1 percent) was kept in a fluid state at 50°C . in a water bath throughout the test. Nutrient agar was dissolved in distilled water (0.15 cc. of 1.6-percent) and placed in a 10-mm. test tube. Immune sera (0.35 cc.) was added. The contents were mixed and tubes placed in the refrigerator for hardening. Then 1.0 cc. of 0.8-percent merthiolate agar was poured over this first layer and the tubes were placed again in the refrigerator to set. Dialyzed antigen (0.5 cc.) containing about two-percent total solids was then added. The tubes were plugged with cotton wool and kept in the refrigerator for two days, after which they were sealed with parowax and incubated at 37°C . The tubes were observed daily up to 15 days.

ELECTROPHORETIC PROCEDURE

Using the technique of Durram (Spinco), electrophoretic studies were carried out on the corneal extracts which had been made up for the intravenous injections, and on all rabbits normal and immune sera. These specimens (0.1 cc.) were applied to Whatman 3.0-mm. paper strips, and the protein fractions separated by allowing electrophoresis to proceed overnight (16 hours). A constant current of five milliamperes per cell was maintained, using the barbituric buffer at pH 8.6. The strips were dyed with bromophenol blue.

RESULTS

1. GEL DIFFUSION ANALYSIS

Antisera from rabbits which had been immunized with fresh whole bovine corneal

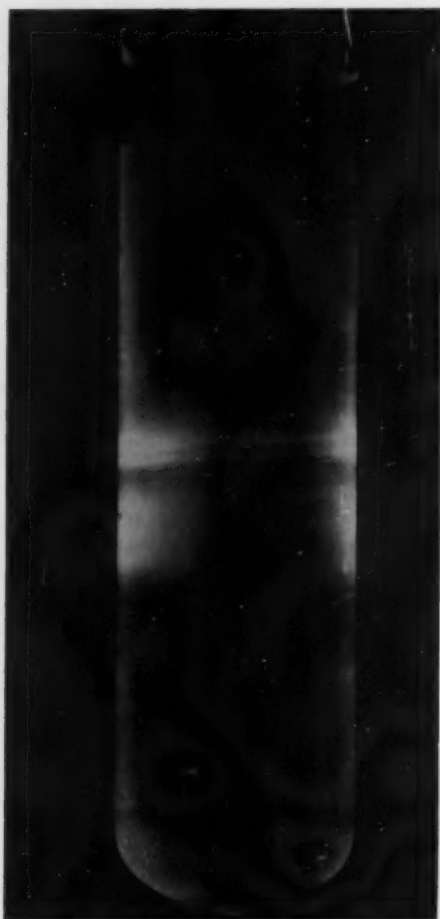


Fig. 1 (Fielding, Basu and Ormsby). Antigen-antibody bands by gel diffusion technique.

extract formed five bands with the whole bovine corneal extract (fig. 1), four bands with extract made from fresh bovine cornea without epithelium, five bands with extract made from bovine cornea stored at -79°C . (except that one band was more intense) and six bands with extract made from bovine cornea stored at 4°C .

Antisera from rabbits immunized with soluble bovine mucoïd fraction formed three bands with all bovine extracts except collagen (table 1).

Antisera from rabbits which had been immunized with extract made from fresh

bovine cornea without epithelium, gave two very faint bands with all bovine extracts except collagen.

Antisera from rabbits immunized intraperitoneally with a larger dose of extract made from fresh bovine cornea without epithelium, gave the same main bands as antisera from rabbits immunized by intravenous injections of extract made from fresh whole bovine cornea (with epithelium) except that the bands were not so intense and the faint bands were not present.

Antisera from rabbits immunized with extract made from whole bovine cornea stored at -79°C . gave six bands with extract from fresh whole bovine cornea and with extract made from bovine cornea stored at -79°C ., three bands with the soluble mucoïd fraction, five bands with extract made from fresh bovine cornea without epithelium, and five bands with extract made from bovine cornea stored at 4°C .

Antisera from rabbits immunized with extract made from bovine cornea stored at 4°C . formed four bands with extract made from fresh whole bovine cornea and with extract made from bovine cornea stored at -79°C ., three bands with soluble mucoïd fraction and with extract made from bovine cornea stored at 4°C ., and four bands with extract made from fresh bovine cornea without epithelium.

Antiserum prepared from homologous rabbit corneal extract did not develop any precipitation bands with its own antigen or with any other heterologous antigens used in this study. Nor did bovine collagen or the phenol insoluble fraction containing mucoïds show any bands by this method with this antiserum.

RESULT OF ELECTROPHORESIS

All antisera which formed antigen-antibody bands by Oudin's gel technique showed (by electrophoresis) an increase in the gamma globulin fraction as compared with the sera taken before immunization (figs. 2a and 2b).

Saline soluble extract from bovine fresh

TABLE 1
ANTIGEN-ANTIBODY PRECIPITIN BANDS PRODUCED BY CORNEAL EXTRACTS
(Oudin's gel diffusion technique)

Bovine Extracts (antigen)	Antisera from Rabbits (antibody) Immunized with	Bands			
		Total	Intense	Medium	Faint
Whole fresh cornea	Extracts from whole fresh bovine cornea	5	2	2	1
Cornea without epithelium		4	2	2	—
Soluble mucoids		4	—	2	2
Stored at -79°C .		5	2	2	1
Stored at 4°C .		6	2	2	2
Whole fresh cornea	Extracts from fresh bovine cornea without epithelium	2	—	—	2
Cornea without epithelium		2	—	—	2
Soluble mucoids		2	—	—	2
Stored at -79°C .		2	—	—	2
Stored at 4°C .		2	—	—	2
Whole fresh cornea	Soluble mucoids from fresh bovine cornea	3	—	2	1
Cornea without epithelium		3	—	2	1
Soluble mucoids		3	—	2	1
Stored at -79°C .		3	—	2	1
Stored at 4°C .		3	—	2	1
Whole fresh cornea	Extracts from bovine cornea stored at -79°C .	6	2	1	3
Cornea without epithelium		5	2	—	3
Soluble mucoids		3	2	—	1
Stored at -79°C .		6	2	1	3
Stored at 4°C .		5	2	—	3
Whole fresh cornea	Extracts from bovine cornea stored at 4°C .	4	2	—	2
Cornea without epithelium		4	2	—	2
Soluble mucoids		3	2	—	1
Stored at -79°C .		4	2	—	2
Stored at 4°C .		3	2	—	1

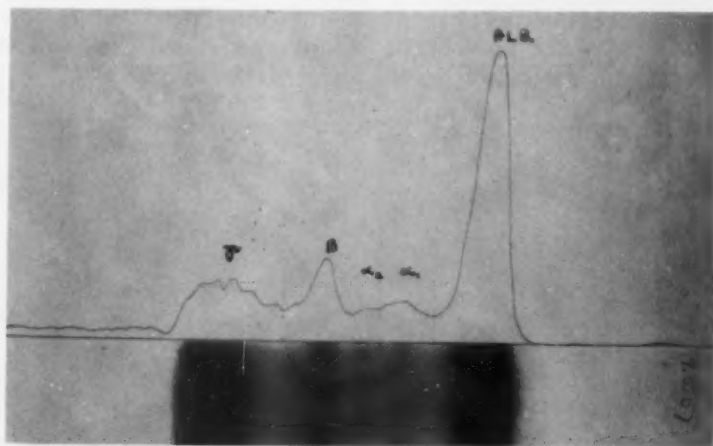


Fig. 2a (Fielding, Basu and Ormsby). Electrophoretic pattern of rabbit's normal serum.

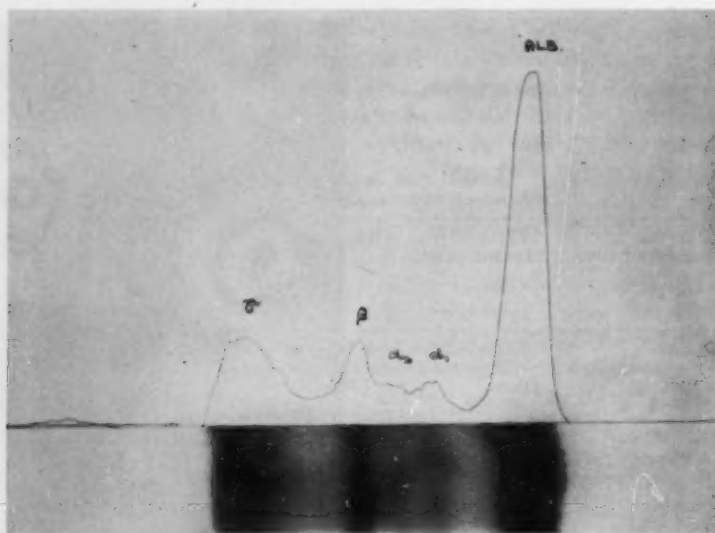


Fig. 2b (Fielding, Basu and Ormsby). Electrophoretic pattern of rabbit's antiserum to whole bovine extracts (increase in globulin fraction).

whole cornea showed three fractions by electrophoresis, but when the protein concentration was increased, two more fractions were obtained, one of which (fraction I) has been shown to contain the acid mucopolysaccharide¹ (Smith and Woodin) (figs. 3a and 3b). Extracts from bovine cornea without epithelium showed five fractions similar to those in whole cornea, but fractions I and II were more concentrated and fractions III and IV were in lower concentration (fig. 4).

Fraction V was very difficult to compare because of the presence of denatured protein. Protein extracts with high antigenic properties (by gel diffusion) showed an increase in protein fractions III and IV by electrophoresis.

Rabbits' corneal extracts also showed five fractions by electrophoresis and there was only slight difference between the extracts of whole cornea and cornea without epithelium (figs. 5a and 5b).

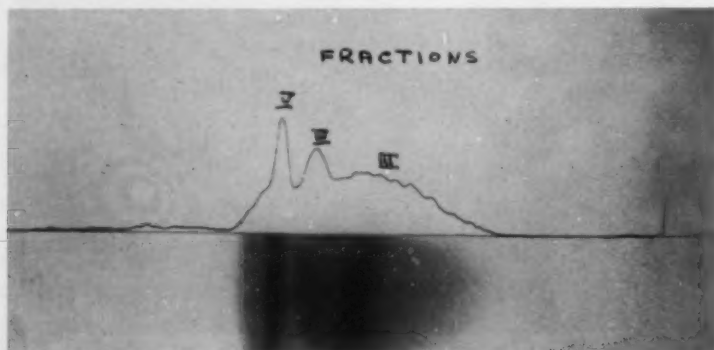


Fig. 3a (Fielding, Basu and Ormsby). Electrophoretic pattern of extracts made from whole fresh bovine cornea.

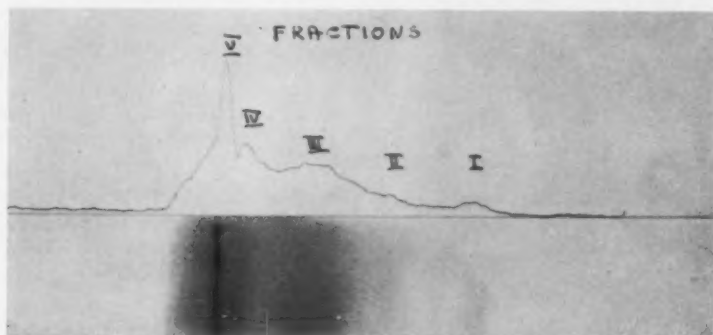


Fig. 3b (Fielding, Basu and Ormsby). Electrophoretic pattern of whole fresh bovine corneal extracts containing a high concentration of protein.

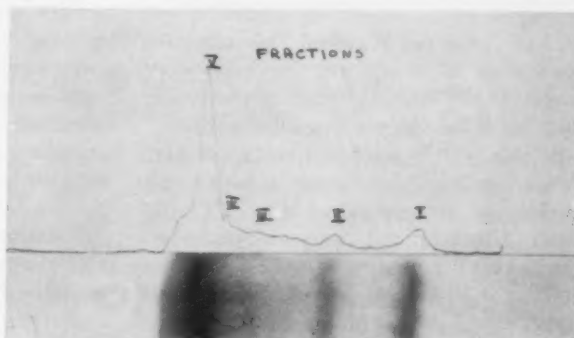


Fig. 4 (Fielding, Basu and Ormsby). Electrophoretic pattern of extracts made from fresh bovine cornea without epithelium.

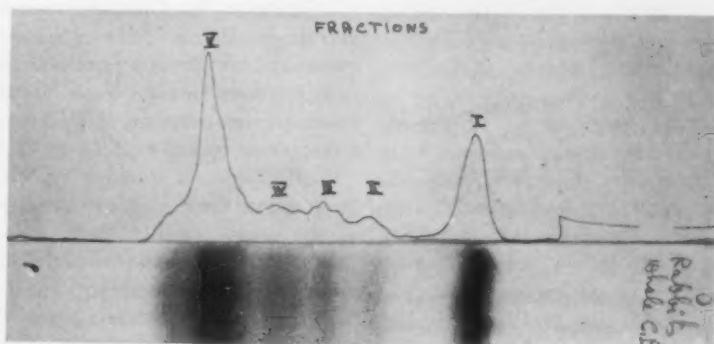


Fig. 5a (Fielding, Basu and Ormsby). Electrophoretic pattern of extracts made from whole fresh rabbits' cornea.

DISCUSSION

Failure of collagen in these experiments to stimulate antibody formation may have considerable significance because of the high

concentration of this substance in the cornea.

Our demonstration of antigenicity in soluble mucoid extracts of cornea confirms the

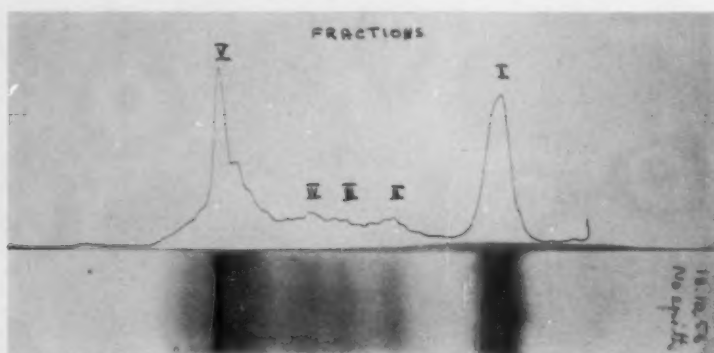


Fig. 5b (Fielding, Basu and Ormsby). Electrophoretic pattern of extracts made from fresh rabbits' cornea without epithelium.

work of Smith and Woodin.³ This may have significance in corneal grafting in view of the role of the corneal mucoids in preventing vascularization (Meyer and Chaffee) 1940.⁸

Soluble protein fraction from whole beef cornea was highly antigenic in both fresh corneas and in those stored at -79°C . (60 days). However, this antigenicity was altered when the corneas were stored at $+4^{\circ}\text{C}$. for 30 days. In previous experiments tissues stored at -79°C . were less antigenic than fresh cornea when used in interlamellar grafts.⁹ This discrepancy may be due to the loss of epithelium during surgery in the previous experiments, whereas epithelium was not lost in this work.

The higher concentration of antigen in epithelium may have great significance in corneal grafting since it is possible to denude this layer from the donor cornea at the time of operation. Experimentally in rabbits we have previously shown that removal of epithelium from donor cornea used for lamellar and interlamellar grafts reduced the incidence of reactions.⁹

Species differences in the soluble protein

fractions, both in concentration and in nature, suggest that further investigation might eventually reveal a cornea from an animal source which might be useful in transplantation to human eyes.

SUMMARY

1. Antisera were prepared by immunizing rabbits with corneal extracts, and the antigen-antibody systems were studied by electrophoresis and gel diffusion techniques.

2. Collagen was found to be nonantigenic.

3. Antisera from rabbits immunized with extracts made from homologous whole fresh cornea did not develop detectable antibodies.

4. Extracts made from fresh bovine whole cornea were more antigenic than extracts from cornea without epithelium.

5. Beef corneas stored at -79°C . did not seem to lose their antigenic properties appreciably.

6. Beef corneas stored at 4°C . had a changed electrophoretic pattern and altered antigenic characteristics.

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STUDIES ON THE ANTIGENICITY OF CORNEAL HETEROGRAFTS*

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In a previous study¹ it was observed that human and beef corneal donor tissues remained transparent on successive interlamellar and lamellar retransplantation on rabbits, following in-vivo storage within the intra-corneal space of rabbit's eye. It was also noticed that there was a reduction of the antigenicity of the in-vivo stored corneal donor materials when they were used for grafting, suggesting that a change had occurred in the corneal proteins during the storage. There were at least two possible means by which this might have occurred—either the corneal antigens were associated with the soluble protein fractions and were dissolved out during in-vivo storage, or they were associated with the corneal epithelium which was usually lost during storage, and was not present in the graft at the time of retransplantation.

Precipitation tests have been in use for many years to identify blood, blood stains and meat, and also in the study of animal relationship and evolution.² Human and beef tissues can be readily identified by means of the precipitation test, using antihuman and anti-beef sera.

The present study was carried out to determine if the species-specific antigen of human and beef corneal tissues identifiable by the precipitation test, could be modified by

in-vivo storage of the tissues in the interlamellar space of rabbit's cornea.

METHODS AND MATERIALS

Antihuman and anti-beef sera (prepared from the blood of rabbits hyperimmunized with the whole human and beef sera) were procured from Burroughs Wellcome and Co., England. To check the potency of these antisera at each precipitation test, normal human and beef sera were used as a positive control, and normal rabbit sera were used as a negative control. By a series of preliminary experiments, it was found possible to make antigenic extracts from human and beef corneal tissues (both fresh, and stored at -79°C . up to a period of two years) which gave a positive precipitation reaction with the corresponding antiserum. It was also noted that the presence or absence of the epithelium from the corneal tissue prior to the extraction of the proteins did not alter the antigenicity of the extracts qualitatively in the precipitation test. The optimum concentrations of the tissue extracts and the antisera were determined in a series of preliminary tests.

Full-thickness corneal discs, 10 mm. in diameter, were cut from each human eye and from some of these the epithelium was removed. Each of these corneal discs was then divided into four equal parts, two of which were grafted interlamellarly in both eyes of

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a rabbit, and the other two pieces were stored in a deep freeze at -79°C . Similarly, there were cut from a single beef cornea, four full-thickness discs 6.1 mm in diameter, and four lamellar discs 6.1 mm. in diameter by 0.5 mm. in thickness. Some of the beef corneas were devoid of epithelium. Two full-thickness discs of the beef cornea were grafted interlamellarily into both eyes of a rabbit, and two lamellar discs into both eyes of another rabbit. The remaining two full-thickness and two lamellar beef corneal discs were stored at -79°C .

For subsequent identification of the interlamellarily grafted corneal tissue, a small piece of No. 6-0 black silk thread was introduced within the transplant prior to its insertion within rabbit's intracorneal space.

For each piece of the interlamellar human and beef heterograft, an identical piece of deep-frozen tissue from the same donor served as the control. The storage period of the interlamellar grafts and their controls at -79°C ., varied up to five months. At different intervals, a rabbit was killed and the two interlamellar grafts were dissected out. At the same time, the corresponding control frozen tissues were removed from the storage at -79°C . Extraction of protein from the grafted and the control frozen tissues was carried out for 48 hours at 4°C . in 0.5 and 1.0 ml. of saline, following which the precipitation tests were done.

Six 10-mm. test tubes, containing 0.2 ml. of solution, were used for each test; two for the grafted tissue in two concentrations, two for the control tissues in two concentrations, one for the positive, and one for the negative control. Positive and negative controls were diluted 1:1000 in saline. Using a very fine tipped pipette, 0.1 ml. of the undiluted antiserum was added underneath the extracts and control sera, taking care to avoid mixing. Positive reactions were noted by a precipitation ring at the line of contact. Absence of a precipitation ring within 20 minutes was considered as negative. All tests with negative results were repeated, using a slide

method. One drop of extract was added to a drop of undiluted antiserum on a glass slide, and the mixture was examined under a microscope for any precipitation reaction. In all instances, the slide method verified the results obtained by the test-tube method.

RESULTS

All extracts made from the control frozen human and beef tissues gave positive precipitation reactions. Absence of the epithelium from the tissues prior to extraction did not make any differences qualitatively, and extracts from lamellar tissues were found to be as effective as those from full-thickness tissues. Extracts made from the interlamellar human and beef grafts gave positive and negative results depending on the period of in-vivo storage, but not on the type of the graft (lamellar or full-thickness) or on the presence or absence of the epithelium.

Loss of the species specific antigen from the human and beef grafts was very rapid. Within two weeks after interlamellar grafting, the corneal extracts made from the human and beef heterografts ceased to give positive precipitation reactions with the corresponding antihuman and antibeeff sera, whereas the extracts made from the control frozen tissues always gave positive reactions. With beef heterografts the loss of antigenicity from the lamellar corneal tissues was faster than that from the full-thickness grafts. In general, the results obtained with the human tissues agreed with those with beef tissues, the loss of the species specific antigen being complete within a period of two weeks of in-vivo storage in both types of tissues.

DISCUSSION

These studies have indicated to us that the species specific antigen and the graft-reaction antigen are probably not identical. This is borne out by the findings that the species specific antigen disappears within two weeks of grafting, whereas graft reactions usually take place after this interval. Moreover, the

epithelium apparently provides the larger portion of the graft-reaction antigen,¹ whereas both stroma and epithelium seem equally responsible for the species specific antigen. Deep freezing of donor tissues does not appear to alter the species specific antigen, whereas we have noted in previous work³ that the storage of donor corneal tissues reduced the incidence of graft reactions following transplantation.

Although the biologic nature of the grafted tissues following in-vivo storage is unknown at this time, it would appear that this method of storage could be used for the pretreatment of donor tissues to reduce antigenicity.

CONCLUSIONS AND SUMMARY

Extracts made from human and beef cor-

neal tissues, biologically pretreated in the intracorneal space of the rabbit's eye for two weeks, or more, failed to give positive precipitation reactions with the corresponding antiserum. Extracts made from control tissues stored at -79°C . gave positive reactions with these antisera.

Since the loss of the species specific antigen was complete within two weeks of in-vivo storage, it seems probable that this antigen is not responsible for the donor-recipient reaction (which usually occurs after two weeks of in-vivo storage).

In-vivo storage of corneal heterografts in the rabbit's intracorneal space reduces the antigenicity, with reference both to the species specificity and the donor-recipient reaction.

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SEX CHROMATIN AS A BIOLOGIC CELL MARKER*

IN THE STUDY OF THE FATE OF CORNEAL TRANSPLANTS

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The fate of the cellular elements in grafts has been studied by many methods since the turn of the century. These methods have included histologic investigations aimed at the identification of the graft from the host tissue.¹⁻³ Recently, radioactive tracer substances have also been used for this purpose.⁴ In spite of these studies, little is yet known about the fate of the corneal stroma cells of the graft, largely because of the difficulty in marking the individual cells.

Since the discovery of the sex chromatin in female tissues by Barr and Bertram,⁵ attempts have been made to use the sex chro-

matin as a biologic cell marker in studies on the fate of tissue transplants.⁶ In most tissues, with the exception of nerve cells, the sex chromatin lies peripherally on the nuclear membrane and is about one μ in diameter. The only body of comparable size within the nucleus is the nucleolus, from which the sex chromatin can be readily differentiated by means of specific DNA stain. In general, in female tissues, sex chromatin is present in more than 50 percent of cells, whereas in male cells it is nearly always present in less than five percent.⁷

The main obstacle in applying this technique to the study of corneal transplantation has been the difficulty in visualizing the sex chromatin in ordinary histologic prepara-

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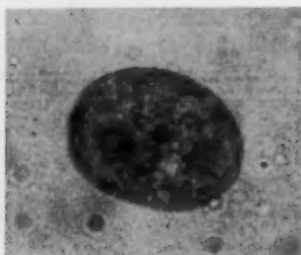


Fig. 1 (Basu, Miller and Ormsby). Nucleus of a corneal stroma cell in tissue culture, showing the characteristic Feulgen-positive sex chromatin at the periphery. The tissue was obtained from a three-month-old graft from a female donor onto the male cat No. 6. ($\times 1,200$.)

tions of the corneal stroma cells which are compressed and twisted in the stromal fibers, thus obscuring the details of the nucleus.

In the present investigation we have developed a technique for the identification of the sex chromatin in the corneal stroma cells, and have used this in the study of the fate of corneal tissues grafted onto recipients of the opposite sex.

METHODS AND MATERIALS

Corneal donor tissues were obtained from normal adult male and female cats and grafted onto recipients of the opposite sex, both by penetrating and lamellar techniques. Penetrating and lamellar grafts were 6.1 mm. in diameter and the lamellar discs were 0.6 mm. in thickness. The recipient cats were killed at different intervals. From all grafts the central five-mm. portion was removed (the lamellar grafts were dissected at a depth of 0.3 mm.), taking care not to include any host tissue. Corneal epithelium and endothelium were thoroughly scraped from the grafts. Along with each piece of corneal stromal tissue removed from the graft for tissue culture, an identical piece of tissue was obtained from the corresponding host cornea to run as the control.

In order to obtain a monocellular layer, graft and control tissues were implanted in Carrel flasks and grown in tissue culture medium at 37°C . When the outgrowth of

cells from the explant was six mm. or more, the culture was trypsinized. The subcultures were then grown on a small section of coverslip introduced within the flask.

All fixation and staining of the subcultured cells were done within the flask in preference to removing the slide prior to the histologic procedure. Fixation was carried out for three hours in modified Davidson's fixative. The cells were stained by modified Feulgen method for one to two hours, and this was followed by counterstaining with light green for approximately 30 seconds. The coverslip containing the cells was then removed from the flask and mounted onto a No. 0 coverslip with Gurr's mounting media, and secured by remounting onto a glass slide for microscopic examination.

RESULTS

In Table 1, it will be seen that in the control female tissues the percentage of cells with sex chromatin, was approximately 45, whereas in the male tissues it was nil.

In the grafted tissues, the male and female sex characteristics (figs. 1 and 2) were retained up to a period of at least three months in clear corneal homotransplants, (cat Nos. 1, 4, 6, 11). After this period the increase of the percentage of sex chromatin in the cells in the male graft (cat No. 5) suggested that there was some invasion of the graft by the host tissue.

The sex difference between the graft and

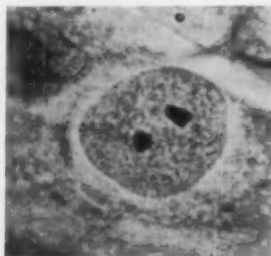


Fig. 2 (Basu, Miller and Ormsby). Nucleus of a corneal stroma cell of male cat No. 6 in tissue culture, showing the absence of sex chromatin. The two central spots are Feulgen-negative. ($\times 1,200$.)

TABLE 1
PERCENTAGE OF CELLS WITH SEX CHROMATIN IN CLEAR CORNEAL HOMOGRAFTS
AND IN THE CONTROL RECIPIENT TISSUES

Recipient Tissue (control)			Grafted Tissue			
No. of Animal	Sex of Host	Sex Chromatin Percentage	Sex of Donor	Type of Graft	Age of Graft in Months	Sex Chromatin Percentage
Cat 1	Female	45	Male	Penetrating	3	0
Cat 4	Female	43	Male	Lamellar	2½	0
Cat 5	Female	45	Male	Lamellar	4½	15
Cat 6	Male	0	Female	Lamellar	3	47
Cat 11	Male	0	Female	Lamellar	1	45

the host tissue does not appear to have any adverse effect on the transparency of the grafts.

DISCUSSION

From this brief study, using clear corneal grafts in cats, it appears that the use of sex chromatin as a biologic cell marker may be helpful in further studies of the fate of transplanted cells in human corneal grafts. Tissues removed in those cases requiring retransplantation would be a source of material for such studies.

SUMMARY

Corneal grafting was performed in cats, using donors and recipients of the opposite

sexes. From graft and corresponding host tissues, corneal stromal cells were obtained as a monocellular layer in tissue culture, and the percentage of the sex chromatin in both graft and host tissues was determined. It was observed that for a period of at least three months, the sex characteristics of a graft remained unaltered. There was some evidence that a slow invasion of the graft with the host tissue might occur after this period.

Corneal grafting with donor material from one sex onto a recipient of the opposite sex did not have any immediate adverse effect on the clarity of the transplant.

Banting Institute (5).

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AN INITIAL EVALUATION OF (ARISTOCORT®) TRIAMCINOLONE AND ITS ACETONIDE DERIVATIVE IN THE THERAPY OF OCULAR INFLAMMATION*

PART II. CLINICAL STUDIES

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Comparative studies of various corticosteroids in experimental rabbits (Part I), demonstrated that the efficacy, potency, and nontoxicity of triamcinolone free alcohol in blocking the five profiles and features of the inflammatory response observed with moderate and severe types of uveitis. The triamcinolone free alcohol was used for parenteral administration on a weight basis giving the highest dosage levels in continuing adequate doses for a short-term therapy. On this criteria, only some of these results may be of therapeutic value to the present clinical problems.¹

This study was conducted to determine the effects of oral administration of triamcinolone free alcohol and the value of its derivative, triamcinolone acetonide topical preparations in the treatment of ocular inflammations.

METHODS AND MATERIALS

Administration was topical and oral. For topical use, two concentrations of micronized triamcinolone acetonide (0.1 and 0.2 percent), with and without combination of neomycin sulfate (0.5 percent), in suspension and ointment forms were available. Hydrocortisone acetate (1.0 percent) was used in suspension form without antibiotics. The triamcinolone acetonide ophthalmic sus-

pensions were available in sterile light mineral-oil base, the hydrocortisone in sesame oil, and the ointment in sterile light mineral oil, anhydrous wool fat (lanolin), and petrolatum alba base.

All these preparations were sterile and uniformly concentrated without muco-ulceration, crystal deposition in the tissues, or caking about the lid margins and fornices. No side-effects or any toxic reactions were observed, except for temporary blurring of vision. Any such suspensions or ointments often cover the anterior surface of the eye somewhat longer than do preparations in aqueous suspension, perhaps widening and prolonging therapeutic action.

The oral triamcinolone free alcohol therapy, which was administered for initial suppression of the acute disease, ranged from 10 to 20 mg. daily for seven to 10 days, depending upon the intensity and character of the ocular inflammatory lesions. When the acute manifestations of ocular lesions subsided, the average daily maintenance dosage used was from 4.0 to 12 mg. The total daily dosage was divided into two to four doses and was given after meals and at bedtime. The maintenance level was reached by reducing the total daily dose by decrements of 2.0 mg. every third day.

Since there were marked individual variations, the change from other corticosteroids to triamcinolone was guided by such general rules as: (1) cortisone (1/6): 60 mg. approximately equivalent to 10 mg. of triamcinolone; (2) hydrocortisone (1/6): 60 mg. approximately equivalent to 10 mg. of triamcinolone; (3) prednisone or prednisolone ($\frac{1}{2}$): 20 to 40 mg., approximately equivalent to 10 to 20 mg. of triamcinolone therapy.

For topical therapy, a small quantity of

* From the Eye Research Section, Department of Surgery, Georgetown University Medical Center. The Research Fellow in Ophthalmology (Dr. Chavan) was supported by the Lions 22-C, Eye-Bank and Research Foundation, Washington, D.C. The research related to this study was supported in part, and the Triamcinolone (Aristocort®) preparations supplied, through the courtesy of Dr. Christopher H. Demos, Medical Research Section, Lederle Laboratories, a division of American Cyanamid Company, Pearl River, New York.

suspension or ointment was instilled into the lower cul-de-sac of the affected eye, three to four times daily or every two hours depending upon the severity of ocular inflammation. The more frequent the topical administration, the better the response noted in many ocular inflammations, especially when the combination of triamcinolone acetonide with neomycin was used. The ointment was instilled at bedtime.

In cases of corneal transplantations, the triamcinolone acetonide ointment was used after removal of silk sutures on the 11th or 15th postoperative day when wound healing was completed. The postoperative reaction rapidly subsided, and in these cases the suspension or ointment was used more frequently, that is, every two hours. The operated eye was left open on the 15th postoperative day. The antibiotics were used in conjunction with triamcinolone oral or topical therapy as necessary.

The duration of topical and oral therapy varied from five days to four months. The patients were observed in the eye clinic or in private practice (Dr. Cummings) at regular intervals during the period of therapy and notations were made regarding their progress.

CLINICAL RESULTS

The cases were classified into three groups and the comparative analysis of results of 133 consecutive eye cases treated with triamcinolone preparations are listed in Tables 1, 2, and 3. The three groups, under the following headings, are discussed in more detail later:

1. Response of anterior segment diseases (table 1).
2. Response of posterior segment diseases (table 2).
3. Response of traumatic and postoperative conditions (table 3).

I. RESPONSE OF ANTERIOR SEGMENT DISEASES

In this group a comparative analysis of

results of 98 consecutive cases treated with triamcinolone acetonide preparations and hydrocortisone topical therapy are listed in Table 1.

Blepharitis. Eight cases of marginal blepharitis and blepharoconjunctivitis were treated with triamcinolone-neomycin ophthalmic suspension and ointment (0.1 or 0.2 percent) and four were treated with hydrocortisone suspension (1.0 percent). All of them had an almost immediate good response to the triamcinolone-neomycin therapy with paling, lessening of lid edema, scaling, marginal irritation and marked decrease in conjunctival congestion. All of the patients recovered within a week but the treatment was continued for an additional five to seven days.

The ophthalmic suspension was instilled three to four times a day and the ointment was used at bedtime. Two of these cases required lid massage and expression of meibomian secretion, and were treated with triamcinolone-neomycin ointment with good results. Four cases were treated with hydrocortisone suspension with poor results; presumably an antibacterial agent was needed.

Acute, subacute and recurrent allergic *catarrhal and follicular conjunctivitis*. In this series 24 cases of unilateral and bilateral, acute, subacute or recurrent conjunctivitis of various types were treated. Eight cases of allergic conjunctivitis cleared almost completely in 24 to 48 hours after triamcinolone (0.1 or 0.2 percent) topical therapy. Of the four patients treated with hydrocortisone suspension (1.0 percent), two were cured within 72 hours, but two cases failed to respond to the same treatment; otherwise, almost complete improvement without recurrence was noted in this group. The local therapy was continued for seven to 10 days more after clearing.

Similar satisfactory response with triamcinolone-neomycin suspension (0.1 percent) was observed in four cases of catarrhal and four cases of follicular conjunctivitis within

TABLE 1
RESPONSE OF ANTERIOR SEGMENT DISEASES
(Comparative analysis of results of 98 consecutive eye cases treated with triamcinolone preparations* and hydrocortisone topical therapy†.)

Diagnosis	Duration of Episode	No. of Cases Treated with Triamcinolone*	No. of Cases Treated with Hydrocortisone†	Results	Remarks
1. Blepharitis	3-12 da.	4	2	Improved	Triamcinolone-neomycin #5 gave dramatic relief of symptoms. Hydrocortisone 1.0% had less influence in one case; presumably, antibacterial agent was needed
2. Acute meibomitis	1-3 da.	5	0	Good	All needed incision, drainage and local antibacterial therapy. Lid and conjunctival reaction responded to triamcinolone-neomycin #5 treatment
3. Blepharoconjunctivitis	3-15 da.	4	2	Excellent	Triamcinolone-neomycin #5 and #6 exerted a rapid ameliorating influence on lid-conjunctival infections and allergic reactions. Hydrocortisone 1.0% failed to improve the condition in one case; presumably, antibacterial agent or desensitization was needed
4. Ocular sensitivity (seasonal, drugs, asthma, hay-fever, and rhinitis)	3 mo.-2 yr.	5	3	Good	Rapid improvement was observed with triamcinolone #1 and #3, and 1.0% hydrocortisone suspension. The symptoms lessened rapidly in all cases
5. Recurrent allergic conjunctivitis (house dust, face powder and other cosmetics etc.)	4 da.-6 mo.	8	4	Improved	Failed to improve on hydrocortisone 1.0% and systemic antihistamine in two cases. Improved on triamcinolone #1 and #2 dramatically in 24 to 48 hours and no recurrence in 3 months
6. Catarrhal conjunctivitis	3-7 da.	4	2	Excellent	Eye condition was refractory to hydrocortisone 1.0%. Triamcinolone-neomycin #5 local therapy gave immediate relief of symptoms with rapid improvement
7. Follicular conjunctivitis	3 da.-2 wk.	4	2	Good	Triamcinolone-neomycin #5 relieved the symptoms in all cases, but the hydrocortisone 1.0% responded poorly
8. Chronic conjunctivitis	3 mo.-2 yr.	2	1	Improved	Marked improvement on triamcinolone-neomycin #6, and fair response on hydrocortisone 1.0%
9. Subconjunctival hemorrhage	1-3 da.	3	0	Improved	The subconjunctival hemorrhage completely cleared in 3-5 days with local use of #2, and #4

* Triamcinolone preparations (Lederle): #1 = Triamcinolone acetonide 0.1% ophthalmic suspension
 #2 = Triamcinolone acetonide 0.2% ophthalmic suspension
 #3 = Triamcinolone acetonide 0.1% ophthalmic ointment
 #4 = Triamcinolone acetonide 0.2% ophthalmic ointment
 #5 = Triamcinolone acetonide 0.1% with Neomycin sulfate 0.5% ophthalmic suspension & ointment
 #6 = Triamcinolone acetonide 0.2% with Neomycin sulfate 0.5% ophthalmic suspension & ointment
 #7 = Triamcinolone acetonide 0.1% topical skin cream or ointment
 #8 = Triamcinolone free alcohol tablets, 2 mg. or 4 mg. each

† Hydrocortisone (Lederle): Hydrocortisone acetate 1.0% ophthalmic suspension

TABLE 1 (continued)

10. Recurrent conjunctivitis (atopic and contact dermatitis)	3 mo.-5 yr.	4	0	Improved	Skin reaction lessened with triamcinolone #7. The conjunctival chemosis rapidly subsided on #2 and #4, and with systemic triamcinolone #8 in all cases
11. Bilateral erythema-multiforme (Stevens-Johnson disease) typical mucocutaneous lesions involving conjunctiva and cornea (symblepharon)	5 yr.	1	0	Not improved	Several times treated with antibiotics, prednisolone, mucous membrane graft for the separation of lid adhesions. Later lamellar keratoplasty was performed. The donor graft was sloughed out without success. Triamcinolone therapy #6, and #7, and #8 lessened the hypersensitivity reaction of lids, conjunctiva, and skin. Condition remained stand still
12. Keratitis:					
Keratoconjunctivitis	2-7 da.	2	1	Improved	All cases improved dramatically on triamcinolone #5 and hydrocortisone local therapy. Corneal edema, ciliary injections, pain and photophobia subsided with less scarring
Superficial punctate-keratitis	2 da.	2	1	Good	
Marginal ulcer	5 da.	2	1	Improved	
Central ulcer	7 da.	1	0	Good	
Deep keratitis	6 mo.	1	0	Marked	All cases required systemic triamcinolone #8 and local therapy with #2 and #4. The corneal edema, vascularization reduced with less scarring and dramatic visual improvement, except in corneal dystrophy cases required surgery
Metaherpatic keratitis	3 mo.	1	0	Improved	
Rosacea keratitis (acneform)	1 mo.	1	0	Improved	
Zonular (band-shape) Dystrophy	30 yr.	3	0	Not improved	
Bullous keratitis (advanced glaucoma)	1-6 mo.	2	1	Not improved	Local and systemic triamcinolone steroid therapy had no effect on corneal edema, degenerative pannus or on intraocular tension in advanced glaucoma
13. Scleritis (rheumatoid):					
Episcleritis	3 wk.	2	1	Excellent	All cases required systemic triamcinolone #8 and local therapy with #2 and #4. Nodular inflammation of sclera, ciliary injections, pain rapidly subsided in 1 to 3 weeks and the eye remained quiet without any recurrence in 4 month, except in case of scleromalacia perforans an indentation area was left. Hydrocortisone 1.0% local therapy had poor results
Scleritis	2 wk.	2	1	Improved	
Sclerokeratitis	2 wk.	1	0	Marked	
Scleromalacia perforans (nodular type)	2 yr.	1	0	Good	
14. Acute iritis:					
Granulomatous	3 wk.	3	1	Fair	Nongranulomatous iritis improved more than granulomatous iritis. Over half of the cases required systemic triamcinolone #8 and local therapy with #2 and #4 and hydrocortisone 1% suspension. Recurrences were not noticed in all cases within 3 months
Nongranulomatous	1-2 wk.	3	1	Improved	
15. Acute iridocyclitis:					
Granulomatous	10 da. 4 mo.	1	0	Good	Acute attack of granulomatous iridocyclitis was subsided with triamcinolone systemic therapy #8 and local use of atropine and #2. Anterior chamber cleared in 3 weeks and no recurrences noticed in 3 months. Two cases of nongranulomatous acute iridocyclitis had been treated with similar therapy with success in all cases
Nongranulomatous	3 wk. 3 yr.	2	0	Good	
		74	24		

TABLE 2
RESPONSE OF POSTERIOR SEGMENT OCULAR DISEASES TREATED WITH SYSTEMIC
TRIAMCINOLONE FREE ALCOHOL THERAPY

Diagnosis	Duration of Episode	No. of Cases Treated with Triamcinolone*	Results	Remarks
1. Central Serous Retinopathy (Retinal Angiospastic Phenomena)	1 da.	1	Marked	Episode of micropsia, metamorphopsia, positive scotoma with reduced vision in both eyes. Spasms of retinal blood vessels and bilateral macular edema with blebs. Yellowish whitish round and oval dots and pigmented areas were observed. The foci of infection, allergic and toxic state, and vascular instability responded. Vitreous opacities cleared with systemic triamcinolone #8, priscoline and potassium iodide solution for a month and half. Vision improved and no recurrence in 4 months
2. Chorioretinitis (Exudative)	8 da.	1	Good	Vitreous haze, retinal edema and exudates gradually cleared leaving a pigmented patch of chorioretinitis in left eye. Systemic triamcinolone #8, and potassium iodide for 6 weeks was administered. Vision improved to normal
3. Optic Neuritis	1 da.	1	Fair	Sudden episode of loss of vision in right eye blurred disc and congested retinal veins with few retinal hemorrhages and exudates with macular star, and vitreous opacities. Condition gradually improved and fair visual acuity regained, except slight plenness of the disc and sector-shaped visual field defect with triamcinolone oral therapy #8
4. Vitreous Hemorrhage	3 da.	1 — 4	Inconclusive	Sudden episode of loss of vision in left eye and some reduced vision in the right eye. Right fundus showed hypertensive changes grade 2, spasms of retinal vessels, flame shape and punctate hemorrhages and vitreous opacities. The left fundus was not clearly visible, the media was hazy with full of vitreous opacities. Triamcinolone #8, priscoline, and C.V.P. therapy was given for 4 weeks along with serpasil-apresoline. Vision fairly improved in both eyes

* Triamcinolone free alcohol (Aristocort®, Lederle).

eight to 10 days of local treatment; but refractory or poor response was noted in the same conditions treated with hydrocortisone suspension (1.0 percent) without an antibiotic. The local treatment continued for eight to 15 days more in all cases of this group.

Ocular sensitivity, acute and chronic lid and conjunctival allergies. In this group, 11 unilateral and bilateral cases were treated for a moderate to severe type of lid reaction and conjunctival congestion due to drug sensitivity and other conditions (penicillin, sulfacetimide, atropine, asthma, hay-fever, seasonal change, and so forth). Five patients were treated for ocular sensitivity

with local triamcinolone suspension and ointment (0.1 percent) and two were chronic conjunctivitis patients treated with triamcinolone-neomycin suspension (0.2 percent) with marked response in 24 to 72 hours.

Similar responses were noted in three patients with ocular sensitivity treated with local hydrocortisone suspension (1.0 percent); however, one case of chronic conjunctivitis had a fair result. Most cases in this group had rapid relief of symptoms and the local treatment was continued for five to 15 days thereafter.

Acute meibomitis. In five early cases of acute meibomitis local hot compresses and

TABLE 3
RESPONSE OF TRAUMATIC AND POSTOPERATIVE OCULAR DISEASES TREATED
WITH TRIAMCINOLONE PREPARATIONS

Diagnosis	Duration of Episode	No. of Cases Treated with Triamcinolone*	Results	Remarks
Traumatic conditions:				
1. Subconjunctival hemorrhage	1 da.	2	Good	Eye completely cleared with #2 and #4 in 3-5 days
2. Corneal edema following removal of foreign body and laceration with contact glass	1-3 da.	3	Excellent	Corneal edema lessened without scarring with triamcinolone-neomycin local therapy #5
3. Scleritis following removal of partial penetrating foreign-bodies	1 da.	1	Excellent	Pain and redness lessened. Required antibiotics and triamcinolone-neomycin local therapy #5
4. Iritis	1-3 da.	3	Good	Anterior chamber flare and aqueous cellularity cleared and eye quiet with #2 and #4
Surgery				
Major				
1. Corneal edema and iritis following operation for traumatic perforation of cornea and iridectomy for iris prolapse	1 da.	1	Excellent	Postoperative inflammatory reaction rapidly subsided with the use of systemic triamcinolone #8, and #2 and #4 therapy
2. Corneal edema and neovascularization of lamellar grafts for corneal scars	6 mo.-1 yr.	5	Excellent	Postoperative corneal edema and neovascularization suppressed in four cases with clear cornea with #2 and #4 therapy, and in the fifth case the graft became opaque due to deep vascularization under the graft
3. Corneal edema, neovascularization anterior synechia of penetrating grafts for corneal scarring (complication)	6 mo.-1 yr.	2	Not improved	Steroid therapy failed to improve the condition because of postoperative complication, required surgery again
4. Corneal edema, and iritis following mushroom grafts for complicated cases of corneal scars and zonular dystrophy	8 da.-1 mo.	4	Improved	Rapid improvement with triamcinolone systemic and local therapy with #2 and #4 and #8. Postoperative inflammation subsided rapidly and three out of four grafts remained clear
5. Striate keratitis and iritis following cataract extraction	10-12 da.	3	Good	Corneal edema and iritis subsided with triamcinolone-neomycin local treatment #6
6. Strabismus	12-15 da.	1	Improved	Postoperative reaction subsided with local triamcinolone therapy #6
Minor				
1. Pterygium	8 da.	3	Improved	Postoperative inflammatory reaction rapidly subsided with triamcinolone-neomycin local treatment #5
2. Chalazion	3 da.	3	Improved	
		31		

* Triamcinolone preparations (Lederle): Same as Table 1.

antibiotics were tried but all went on to chalazion formation which required incision and drainage. Triamcinolone-neomycin suspension or ointment (0.1 percent) was regularly employed in all cases, 24 to 48 hours after surgical drainage with excellent results. The local treatment was continued for five to seven days postoperatively in all cases.

Subconjunctival hemorrhage. Three elderly patients with unilateral subconjunctival hemorrhage of unknown etiology, involving the bulbar conjunctiva, were treated. There was no history of trauma but hypertensive arteriosclerotic heart disease was present. There was a sudden episode of itching, slight pain, and a large subconjunctival area of hemorrhage. The accumulation of blood under the bulbar conjunctiva was observed by slitlamp examination. These cases were referred to an internist to follow their systemic disease and the local condition was treated with frequent use of cold compresses and triamcinolone suspension and ointment (0.2 percent) at bedtime. Rapid and dramatic absorption of the subconjunctival hemorrhage was noted in 24 to 72 hours and the condition completely disappeared in three to seven days.

Dermato-ocular conditions, atopic and contact dermatitis and erythema multiforme. In this group were five cases of associated dermato-ocular diseases. Two of these cases had generalized atopic dermatitis of three to five years' duration, two cases had contact dermatitis of three to four months' duration, and one case had generalized mucocutaneous lesions of five years' duration. All of these patients failed to improve with previous therapy which included topical and systemic steroids, antihistaminics, and surgery. Triamcinolone, orally and in the forms of 0.2-percent topical suspension and ointment, was used along with triamcinolone 0.1-percent cream skin preparation.

Marked improvement was noticed during the first 10 to 20 days of therapy, with lessening of conjunctival, lid and skin reac-

tions. The topical and systemic therapy was continued for two to three months. Initial systemic therapy was 12 mg. per day and then was reduced to maintenance levels. All cases with atopic dermatitis and contact dermatitis with ocular lesions improved satisfactorily. However, the erythema-multiforme patient had involvement of the conjunctiva and the cornea with formation of adhesions between the lids. She had received antibiotics and other steroids for many months and during the last three months was treated with systemic triamcinolone and topical therapy. The hypersensitivity lesions, membranous conjunctivitis, and hypertrophy of the lids were reduced and the condition then remained static without further improvement.

Keratitis. Nineteen cases were divided into three groups. In the first group were 10 acute cases with various types of superficial corneal lesions (keratoconjunctivitis, superficial punctate keratitis, marginal and central ulcer) of from two to seven days' duration, primarily with unilateral involvement. However, in the second group were six chronic cases with various types of deep corneal lesions (deep keratitis, metaherpetic keratitis, rosacea keratitis (acneform) and zonular dystrophy) from one month to 3 years' duration, with primarily bilateral involvement. In the third group were three cases of bullous keratitis described below.

In the first group, there was pain, redness, photophobia, superficial corneal edema and some loss of vision; the second group had no pain, but there was deep corneal edema with a moderate to severe type of neovascularization involving the corneal and peripheral part of the cornea. The first group was treated for five to 10 days with local triamcinolone-neomycin suspension 0.1 percent and with hydrocortisone suspension 1.0 percent. All cases in this group noticed marked lessening of signs and symptoms with improvement in vision and less scarring.

The second group required a combination of local triamcinolone 0.2-percent sus-

pension and ointment with oral triamcinolone therapy for 15 to 21 days with marked improvement of visual acuity and less scarring. However, the cases with zonular dystrophy required corneal transplantation surgery. The slitlamp observation of corneal edema, neovascularization and opacities showed a gradual subsidence in a majority of the cases, and in one case of deep keratitis, vitamin deficiency was suspected and riboflavin (B_2) administered daily along with triamcinolone systemic therapy. In this case there was dramatic improvement of corneal lesions, lessening of neovascularization, and the improvement in visual acuity from 20/400 to 20/40 was dramatic.

The third group of three cases, with bulbous keratitis due to advanced glaucoma, was treated with local triamcinolone suspension 0.2 percent, and systemic triamcinolone therapy without improvement of corneal edema and degenerative pannus. It was concluded that triamcinolone local or systemic administration had no effect in reducing the intraocular pressure; however, these cases were treated with Diamox and Pilocarpine in the usual manner with reduction of intraocular pressure. The dose of triamcinolone in the last two groups was 12 mg./day initially, and reduced to 2.0 mg. daily.

Scleritis (rheumatoid). In this series we had eight unilateral cases of various types of scleritis (episcleritis, scleritis, sclerokeratitis and scleromalacia perforans) with associated rheumatoid arthritis. The duration of the episode was from two weeks to two years and some had been treated previously with corticosteroids in the form of topical and oral prednisolone therapy with recurrences. Most of these cases had a nodular appearance of the sclera with pain, tenderness, ciliary injection and photophobia. All were treated with hot compresses, frequent instillation of local triamcinolone 0.2-percent suspension, and ointment at bedtime, and with systemic triamcinolone for one to three weeks.

All patients responded very well to the

local and systemic triamcinolone therapy (12 mg./day initially and then reduced to maintenance levels). The nodular area, local signs and symptoms rapidly subsided with no recurrence in three months' follow-up. In a case of scleromalacia perforans, the inflammation subsided and the nodular appearance of the sclera was reduced considerably in size, leaving a small area of indentation. Oral triamcinolone was administered for more than four months in this patient. The marked pigmentation in the lid area was also cleared with the triamcinolone cream skin preparation (0.1 percent).

Acute iritis and iridocyclitis. In this series we had 11 patients with acute granulomatous and nongranulomatous iritis and iridocyclitis. Several of these cases demonstrated certain principles in treating the acute conditions. Hot compresses and the frequent use of topical triamcinolone suspension 0.2 percent every two hours during the day, and ointment 0.2 percent at bedtime, were found to be effective within eight to 10 days, and in some of them a marked anti-inflammatory response was noticed within 12 to 48 hours. Atropine 1.0 percent was used in over half the cases to dilate the pupil and to prevent the posterior synechias and other complications.

The anti-inflammatory response was based upon observations by slitlamp and ophthalmoscopic examination in a manner similar to the animal experiments, and thereby grading inflammatory signs such as: diminution of ciliary injection (ciliary flash), hyperemia of iris and posterior synechias, aqueous flare and cellularity in the anterior chamber, cell deposits on the endothelial surface of the cornea (keratic precipitates), inflammatory exudates in the anterior chamber, and improvement in visual acuity.

Six of the cases of nongranulomatous iritis and iridocyclitis (primary) were found to respond rapidly to triamcinolone systemic and local therapy in eight to 10 days; however, in two cases hydrocortisone suspension 1.0 percent local therapy alone was used

and the improvement was not so rapid. It was evident that a combination of local and systemic treatment was indicated.

Similar observations were made in treating five additional cases of granulomatous iritis with triamcinolone local and systemic therapy, and hydrocortisone local treatment. In all of these cases the course of treatment was from two to three weeks with resulting decrease in pain, headaches, ciliary injections and other signs and symptoms of iritis and iridocyclitis as mentioned above. The eyes were quiescent without any recurrence in three months. The systemic dose level of triamcinolone was 12 to 20 mg. initially per day, and was decreased to 4.0 mg./day for one to two weeks. Any possible etiology of the disease, such as foci of infections, metabolic disorders, and so forth, was attended to as indicated.

2. RESPONSE OF POSTERIOR SEGMENT DISEASES

In this group we had four unusual cases which successfully responded to triamcinolone systemic therapy and other medications as listed in Table 2.

Central serous retinopathy (retinal angiospastic phenomena). A 60-year-old white man had a history of reduced visual acuity and black spots in front of his eyes. He was first examined for his eye condition two years ago and glasses were prescribed. At

that time, media and fundi were normal, except for a few vitreous opacities and mild hypertensive arteriosclerotic fundus changes, with normal visual fields. Previous history revealed that he had suffered from a mild cerebral vascular accident and suffered frequently from food allergies.

On his second visit he complained of a sudden episode of blurring of vision (O.D., 20/60; O.S., 10/400), with 24 hours of duration, micropsia, metamorphopsia, scotoma, and black spots in front of his eyes. The visual acuity with correction did not improve; intraocular pressure in both eyes was within normal limits. Media and fundus examination revealed haziness of the vitreous due to fine opacities, more in the left than in the right eye. Both discs were normal, except for hypertensive arteriosclerotic vascular changes with marked spasm of the superior and inferior temporal branch of the central retinal artery in both eyes, and bilateral macular edema with yellowish bleb formations.

In five to seven days the blebs and macular edema were considerably reduced and yellowish-whitish round and oval dots and pigmented areas appeared. A search for foci of infection and systemic disease was made; laboratory studies of fasting blood sugar and urinalysis were done as well as allergy tests and systemic examination, including blood pressure, and X-ray films of

TABLE 4
KEY TO FIGURES 1-8

Figure No.	Clinical Diagnosis	Treatment	Before Treatment	After Treatment
1 and 2	Marginal blepharitis (lid reaction) (table 1, diagnosis 1)	Triamcinolone acetonide (0.1%) with neomycin (0.5%) ointment (#5)	Fig. 1	Fig. 2 3 days
3 and 4	Ocular sensitivity (table 1, diagnosis 4)	Triamcinolone acetonide (0.1%) with neomycin (0.5%) suspension and ointment (#1 and #3)	Fig. 3	Fig. 4 10 days
5 and 6	Recurrent allergic conjunctivitis (table 1, diagnosis 5)	Triamcinolone acetonide (0.2%) without neomycin, suspension and ointment, triamcinolone acetonide (0.1%) skin cream (#1 and #2)	Fig. 5	Fig. 6 15 days
7 and 8	Chronic conjunctivitis (table 1, diagnosis 8)	Triamcinolone acetonide (0.1%) without neomycin, suspension and ointment (#6)	Fig. 7	Fig. 8 2 days

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Fig. 4
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Fig. 6
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Fig. 8
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Fig. 1



Fig. 2

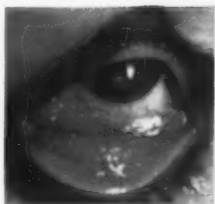


Fig. 3

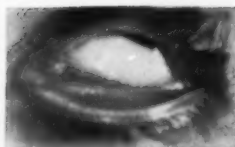


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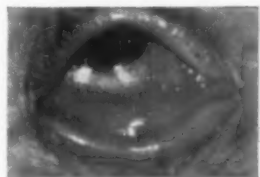


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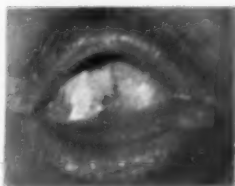


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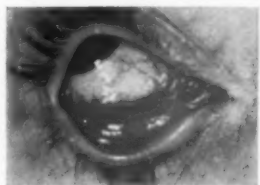


Fig. 7



Fig. 8



Fig. 9



Fig. 10

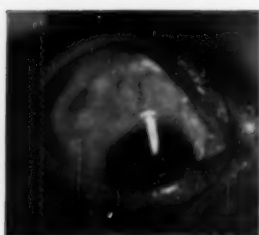


Fig. 11

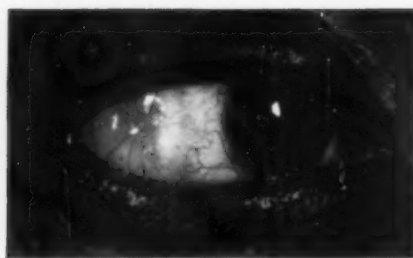


Fig. 12

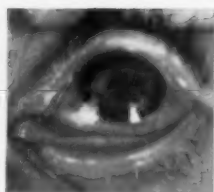


Fig. 13



Fig. 14

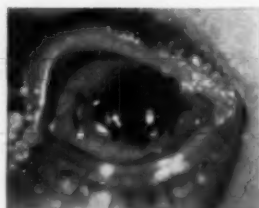


Fig. 15



Fig. 16

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the chest, skull and sinuses. No significant abnormalities were found.

Triamcinolone (20 mg. per day) was given orally along with Priscoline, 25 mg., every six hours for 10 days; then the dose of triamcinolone was gradually reduced to 12 mg. per day and potassium iodine solution (15 drops) was administered twice daily after meals for another three weeks. All the medications were gradually reduced again over a three-month period. During this time the patient felt better and all the signs and symptoms subsided with marked improvement in visual acuity in both eyes (O.D. 20/30; O.S. 20/40, with correction O.D. 20/20; O.S. 20/25), except for a small positive scotoma.

Chorioretinitis (exudative). Another interesting sequence of response was noted in a 36-year-old white woman who complained of headaches, pain, and black spots in front of her eyes, with eight day's duration. The visual acuity was reduced in the left eye (O.D. 20/20; O.S. 20/200). Previous history revealed that she had had rheumatic fever with pain in the joints. Dental examination showed some foci of infection and these were attended to along with her eye

condition. The eye examination revealed cloudy media with whitish serous exudates, fine vitreous opacities, and retinal edema at the far periphery of the left fundus without involving the macular area on the temporal side.

Triamcinolone, orally at a dose of 20 mg. per day, was administered for 10 days and then gradually reduced to 12 mg. a day for another 10 days; then again reduced to 4.0 mg. per day along with potassium iodide solution (10 drops b.i.d.) after meals for additional three weeks. Marked improvement was noted during the first two to three weeks and the vitreous opacities cleared, leaving a patch of chorioretinitis. The central field was not affected and vision improved to normal.

Optic neuritis. The third patient was a 40-year-old white man, who had a history of sudden episode of blurring of vision in right eye (O.D., 10/200; O.S. 20/20) with 24 hours' duration. Fundus changes revealed a markedly hyperemic and blurred disc, elevated less than two diopters, retinal arteries were thin and veins were moderately dilated and tortuous. A few retinal hemorrhages with well-defined spots of exudates were

TABLE 5
KEY TO FIGURES 9-16

Figure No.	Clinical Diagnosis	Treatment	Before Treatment	After Treatment
9 and 10	Subconjunctival hemorrhage (table 3, diagnosis 1)	Triamcinolone acetanide (0.2%) without neomycin, suspension and ointment (#2 and #4)	Fig. 9	Fig. 10 6 days
11 and 12	Scleromalacia perforans (rheumatoid) (table 1, diagnosis 13)	Triamcinolone acetanide (0.2%) without neomycin, suspension and ointment. Triamcinolone acetanide (0.1%) skin cream. Triamcinolone free alcohol tablets (#2, #4 and #8)	Fig. 11	Fig. 12 30 days
13 and 14	Deep keratitis, iritis, riboflavin (B ₂) deficiency, corneal edema, neovascularization and opacities (table 1, diagnoses 13 and 14)	Triamcinolone acetanide (0.2%) without neomycin, suspension and ointment. Triamcinolone free alcohol, tablets. Riboflavin (B ₂) tablets (#2, #4 and #8)	Fig. 13	Fig. 14 21 days
15 and 16	Mushroom graft 10 mm. (central penetrating 7 mm.), corneal edema, neovascularization, and iritis following corneal transplantation, senile cataract (table 3, diagnosis 4)	Triamcinolone acetanide (0.2%) without neomycin, suspension and ointment. Triamcinolone free alcohol, tablets. Multivitamin capsules postoperatively (#2, #4 and #8)	Fig. 15	Fig. 16 21 days

close to the disc, involving the macula, forming a star in the right eye, and a vitreous haze.

Oral triamcinolone, 20 mg. initial dosage per day, was administered for the first week with some improvement in vision; then the dosage was gradually reduced to 12 mg. per day for an additional two weeks, and in the fourth week still further reduced to 8.0 mg. per day, and 4.0 mg. per day for additional two weeks then discontinued. At the end of the six weeks, retinal changes disappeared, except for slight paleness of right disc, and peripheral wedge-shaped visual field defect, his vision improvement dramatically (O.D., 20/70; O.S., 20/20).

Vitreous hemorrhage. The fourth interesting patient was a 60-year-old Negress, who noted sudden loss of vision (O.D., finger counting at six inches; O.S., 20/70) with three days' duration. Vitreous hemorrhages were noted more in the right eye than in the left. Fundus examination revealed marked spasms of the retinal vessels and hypertensive arteriosclerotic grade II changes, with flame-shaped hemorrhages at the superior and nasal area and midperiphery of the fundus. Small, punctate, deep hemorrhages with diabetic exudates surrounded the left macular area and floating vitreous opacities were seen in the left eye. However, the disc in the right eye was not clearly visible because of a hazy appearance of the vitreous, and no fundus details could be seen.

The patient was under medical observation and treated for her hypertensive and diabetic condition. Fasting blood sugar and blood pressure were controlled. Serpasil-apresoline and a small dosage of triamcinolone 8.0 mg. per day with Priscoline, and CVP* were administered for three weeks.

During that time some improvement of

vision was noticed; however, the triamcinolone was reduced to 4.0 mg. per day with frequent checking of fractional urines and fasting blood sugar examinations every other day for another week. The visual acuity improved (O.D., 20/400; O.S., 20/40) after the vitreous opacities cleared and a fair result was obtained with adequate and low dosage of triamcinolone and without any complications.

III. RESPONSE OF TRAUMATIC AND POST-OPERATIVE OCULAR CONDITIONS

In this group a total of 31 major and minor, traumatic and postoperative cases were treated with local and systemic triamcinolone therapy to suppress the postoperative reaction, corneal edema, neovascularization, and iritis, and so forth, as listed in Table 3.

Traumatic complications. In this series were nine cases with traumatic subconjunctival hemorrhage, corneal edema following laceration and removal of foreign bodies from the cornea, traumatic scleritis following removal of partial penetrating foreign bodies (three pieces of wood), and iritis. All of these cases had moderate to severe reaction, pain, ciliary injection, subconjunctival hemorrhages, and some loss of vision.

These conditions were treated with topical instillation of triamcinolone suspensions and application of ointment (0.1 or 0.2 percent) after removal of foreign bodies from the affected eye. Over half of these cases required a combination of triamcinolone-neomycin topical suspension and ointment (0.1 percent). In a case of iritis, and scleritis atropine (1.0 percent) was instilled, and the anterior chamber flare and aqueous cloudiness cleared with relief of signs and symptoms. Lid and conjunctival edema subsided and subconjunctival hemorrhage was rapidly absorbed. All the cases required topical treatment for five to eight days, and marked improvement was noted in 12 to 24 hours.

Major postoperative conditions. In this

*CVP: 100 mg. citrus bioflavonoid and 100 mg. ascorbic acid combined, administered to patient three times a day over a period of three weeks in conjunction with Serpasil-Apresoline (0.2 mg. Serpasil and 50 mg. Apresoline) three times a day and Priscoline (50 mg.) three times a day. (E.J.C.)

group we had 16 major surgical cases operated upon for repair of perforated corneal wound with iris prolapse, corneal edema, neovascularization and iritis following lamellar, penetrating, and mushroom corneal transplantations, and cataract surgery. In the first 10 days after the intraocular surgery, Neosporin ophthalmic solution was instilled; on the 11th or 15th day the corneal sutures were removed, and from the 12th or 16th postoperative day triamcinolone suspension and ointment (0.2 percent) were used to suppress the maximum response.

In corneal transplantation cases, systemic triamcinolone 8.0 mg. per day (with vitamin supplements) was used for the first week, in the second week it was increased gradually to 12 mg. per day, and in the third and fourth week increased to 20 mg. per day, then again gradually reduced to maintenance dose of 4.0 mg per day for two to four months until the donor-recipient reactions were completely subsided. Most of these cases were also treated with steroids previous to the corneal transplantations.

All the cases were examined regularly postoperatively under the slitlamp to evaluate the suppressive effect of triamcinolone preparations on corneal edema, neovascularization, anterior chamber activity, and iritis. In the majority of lamellar and mushroom corneal transplantations, that is, seven out of nine, grafts became completely cleared and vision improved satisfactorily, but in penetrating keratoplasty the grafts became opaque in two cases because postoperative anterior synechias were formed; therefore, these cases required surgery again.

In a case of perforated cornea with iris prolapse, iridectomy was performed, the corneal wound was sutured with silk, and the conjunctival flap was brought over the wound; postoperatively a severe reaction was noted with marked lid, conjunctival and corneal edema and iritis. Triamcinolone, orally, and 2.0 percent locally, was used to suppress the response rapidly with marked

improvement. The eye was quiescent with 20/15 vision. In the case of strabismus, postoperative reaction rapidly subsided with triamcinolone-neomycin suspension (0.2 percent).

Minor postoperative conditions. In this series a total of six minor surgical cases of pterygium and chalazion were treated postoperatively with triamcinolone-neomycin local suspension and ointment (0.1 and 0.2 percent). The postoperative reaction in pterygium was markedly reduced without recurrences in three months' followup.

The examples of the conditions listed in Tables 1 and 3 are best demonstrated in color illustrations before and after treatment with triamcinolone preparations (figs. 1 through 16, tables 4 and 5).

COMMENTS

The anti-inflammatory activity of triamcinolone free alcohol on the basis of animal experimentations was found to be 10 to 20 times more active than cortisone and hydrocortisone, and two to five times more active than prednisone and prednisolone.¹ On this criteria, an intake of 60 mg. per day of cortisone and hydrocortisone, or 20 to 40 mg. per day of prednisone and prednisolone equals 10 to 20 mg. per day of triamcinolone. Although these ratios were established on the basis of animal studies of experimental uveitis, they appeared to be adequate criteria for the administration of therapeutic levels of triamcinolone for the treatment of acute, subacute and chronic inflammatory or allergic ocular lesions in the majority of patients.

A comparison of 0.1 percent and 0.2 percent triamcinolone acetonide topical preparations, with and without Neomycin 0.5 percent, against 1.0 percent hydrocortisone suspension revealed a marked difference in response. In the patients who did not require antibiotic therapy, 0.1 percent and 0.2 percent triamcinolone topical preparations could be compared against 1.0 percent hydrocortisone, and in these patients the triamcino-

lone preparations appeared to be superior. In some patients with severe disease, it appeared that the 0.2 percent triamcinolone acetonide concentration was better than the 0.1 percent.

A group of patients with acute, subacute or chronic conjunctivitis, atopic dermatitis, recurrent allergic conjunctivitis, subconjunctival hemorrhage, superficial or deep keratitis and iritis, responded dramatically to frequent local applications or to treatment with combined local and systemic therapy. Patients who did not respond to older steroids, given topically and/or orally, responded to triamcinolone.

The response of anterior and posterior segment, traumatic and postoperative ocular inflammations, was so impressive that in many cases good results were obtained in patients who were either refractory to or obtained a poor result when treated with the older corticosteroids, including prednisone or prednisolone. The use of triamcinolone, both topical and oral, in these patients produced marked lessening of corneal edema, neovascularization and iritis.

The posterior segment response in ocular diseases treated with systemic administration of triamcinolone appeared to be satisfactory in central serous retinopathy and chorioretinitis, and a fair result was obtained in patients with optic neuritis. There were inconclusive results in patients with vitreous opacities and hemorrhages. It is felt, however, that not enough patients with posterior segment disease have been evaluated to permit a valid comparison of therapy.

The tissue tolerance of triamcinolone preparations to local or systemic administration was good, and the side-effects for short or long-term therapy appeared to be reduced. Synergistic, soothing, and antiphlogistic effects, coupled with prolonged action of the triamcinolone preparation on the inflamed ocular tissues, appeared satisfactory. The oil preparations appeared to keep the steroid in contact with the ocular tissues for a prolonged period of time.

Triamcinolone acetonide was not available for parenteral administration and therefore, the triamcinolone free alcohol preparation was used in the experiments in rabbits.¹ Studies in humans, in which triamcinolone acetonide was compared against triamcinolone free alcohol by the oral route of administration in patients with rheumatoid arthritis and dermatoses indicate that triamcinolone acetonide is probably equal on a molecular basis in anti-inflammatory activity to triamcinolone free alcohol.²

Animal studies, however, indicate that triamcinolone acetonide was four times more active than triamcinolone free alcohol as tested by glycogen deposition and thymus involution in the rats.³ Although the oral activity of the acetonide did not translate from the animal to the human, it has been found by many investigators that the acetonide topically has 10 times or more the activity of hydrocortisone. Other studies indicate that triamcinolone free alcohol topically is equivalent to or, at the most, twice as active as hydrocortisone.

Our studies certainly indicate that triamcinolone acetonide is 10 times more active than hydrocortisone when used topically in treating ocular diseases. It would be of great interest to determine whether triamcinolone acetonide would be 10 times more active than the free alcohol as determined by efficacy in blocking or treating experimental uveitis in animals.

Some adverse reactions due to systemic triamcinolone therapy have been reported in the literature similar to those with prednisone and prednisolone, and some investigators have recommended the drug for short-term therapy.^{3,4} Our experience with low maintenance dosage levels of triamcinolone revealed that the systemic reactions for short or long-term therapy of up to four months duration were minor.

Triamcinolone free alcohol and its derivative, triamcinolone acetonide, both are effective and potent steroids. When administered either systemically or locally (individually

or in combination), early in the course of the disease, the clinical response to these steroids is greater and the incidence of relapses is decreased.

While none of the synthetic steroids is clearly superior to the others, there is at times a striking individual variation in patient response. As far as electrolyte metabolism is concerned, there are some situations wherein one steroid is more efficacious than the other. If the patient tends to have edema in which sodium and fluid retention is apt to be a problem associated with ocular inflammation, triamcinolone is better. If the patient is underweight, weak or debilitated, triamcinolone probably should not be used because of its appetite suppression. On the other hand, it may be helpful to use triamcinolone in the obese arthritic patients having associated ocular inflammation or in those with chronic heart disease or dermato-ocular problems.

TOXICITY

A question may arise as to the mineral oil base in the topical triamcinolone acetate suspensions, as to whether or not there is any possibility of lipoid pneumonia occurring due to the drainage of drops into the bronchial tree by way of the lacrimal passage. It is our opinion that only very small amounts of the oil base might get into the pharynx by this route and that such quantities would probably be insignificant from the standpoint of possible undesirable effects. The patients (from six months to 60 years of age) who were treated with suspensions in either mineral oil or sesame oil base received the preparations from five to 21 days or more up to four months, and had no undesirable side-effects. Local irritation to these topical preparations in both oil suspensions and ointment base was seldom noted on two- to four-hour administration.

Studies of clinical toxicity do not show any unusual side-effects or complications occurring in our patients as a result of systemic triamcinolone therapy. We had better

results in eye patients who had hypertension and chronic nephritis with a unilateral functioning kidney.

The chronic dermato-conjunctivitis patients (atopic dermatitis, contact dermatitis, and so forth) had unusually dramatic skin and ocular responses with a combination of topical and systemic triamcinolone therapy, in contrast to the older steroids and prednisolone which failed to produce a satisfactory response in these chronic conditions.

Salt and water retention was not a problem, and no increases were noted in arterial pressure of patients with uncomplicated hypertension or nephritis who did have salt retention on older steroids. Negative potassium, calcium and nitrogen balances have not been discernible with triamcinolone at adequate therapeutic dose levels. None of our patients experienced dehydration, muscular cramps, protracted weight loss, vertigo or headache. Patients under therapy with triamcinolone exhibited a renewed sense of well-being and appetite was increased. The incidence of side-effects associated with cortisone and hydrocortisone were greatly diminished at the recommended dose levels and there were little or no hypertensive or diabetogenic effects.

The superiority of anti-inflammatory and anti-allergic activity with lower maintenance doses of triamcinolone in clinical studies was increased by the simultaneous administration of an antibiotic agent, multivitamins and other medications, resulting in rapid relief of symptoms, particularly in anterior segment, traumatic and postoperative ocular reactions, as well as in complicated cases of anterior and posterior segment ocular involvement. Since triamcinolone is a potent corticosteroid, however, the usual indications and contraindications should be observed as with cortisone, hydrocortisone, prednisone or prednisolone. In acute infections and complications such as descemetocoele and dendritic keratitis, and so forth, triamcinolone preparations were avoided.

SUMMARY AND CONCLUSIONS

1. Triamcinolone free alcohol (Aristocort®) and its derivative, triamcinolone acetate (Aristocort Acetate), new synthetic steroids, are useful agents in the treatment of anterior and posterior segment ocular diseases, traumatic and postoperative inflammatory ocular conditions.

2. Triamcinolone, used topically in the form of the acetate at 0.1-percent and 0.2-percent concentrations in mineral oil, or in ointment base either alone or in combination with Neomycin 0.5 percent, when employed simultaneously and frequently, exerts an ameliorating and antiphlogistic influence on the course of many ocular infections and allergic reactions with rapid relief of symptoms. Triamcinolone acetate topical preparations at 0.1 percent and 0.2 percent appeared to be 10 times or more superior to hydrocortisone suspension 1.0 percent.

3. Triamcinolone free alcohol, administered systemically, either alone or in combination with topical preparations of triamcinolone acetate, with or without neomycin, produced rapid suppression of inflammatory and allergic disease. Acute, and complicated eye diseases associated with dermatologic conditions, rheumatoid arthritis, hypertensive and mild diabetogenic conditions, which did not respond favorably to older steroids or antihistaminic therapy, did respond favorably to triamcinolone. The anterior segment,

traumatic and postoperative inflammatory diseases responded more favorably than posterior segment ocular diseases.

4. The toxic effects associated with systemic or local use of triamcinolone preparations for short or long-term therapy in continuing adequate low maintenance dosage levels were minimal even in debilitated and elderly patients (vitamin supplemented). Salt and water retention was not a problem with our cases, weight loss and the increased appetite seems to be an individual variation. Tissue tolerance was good and there was not a single instance of undesirable reaction. It appears that triamcinolone is a major advancement in that it has greatly enhanced therapeutic effectiveness with increased glucocorticoid activity and greatly diminished mineralocorticoid activity.

5. Triamcinolone free alcohol and its acetate preparations not only appear to be 10 to 20 times more active than cortisone and hydrocortisone and two to five times more active than prednisone and prednisolone, but along with their anti-inflammatory and anti-allergic activity they appear to have increased efficacy, potency and safety. The high index of therapeutic activity when administered orally and topically make these drugs ideally suitable for use in ophthalmology and they deserve further study in ocular conditions.

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(7)

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ENZYMATIC ZONULOLYSIS*

ALPHA CHYMOTRYPSIN—AN AID TO INTRACAPSULAR CATARACT EXTRACTION

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This report deals with 77 cataract operations performed with the aid of alpha chymotrypsin for enzymatic zonulolysis (method of Barraquer¹) and includes a brief review of the recent related literature. The material used for 75 cases was Alpha Chymar[®] supplied by Armour Pharmaceutical Company. Quimotrase, the Spanish product made by P.E.V.Y.A. Laboratories, was used by me in two cases.

The aim of this new procedure, enzymatic zonulolysis, is to facilitate the separation of the lens capsule from its suspensory ligament for easy lens extraction without producing chemical damage to intraocular tissues. The accomplishment of this purpose would more readily assure the delivery of the cataract within the intact capsule and thus reduce the likelihood of capsular rupture with its attendant complications of retained capsule shreds, iridocapsular adhesions, secondary cataract, postsurgical cyclitis, and the uveitis associated with phacogenic inflammation.

Modern intracapsular cataract surgery safeguards include among other things (1) asepsis, (2) sedation, (3) adequate anesthesia and (4) akinesia (by means of retrobulbar Novocaine, adrenalin, hyaluronidase injection, subconjunctival injection and facial nerve block), (5) softening of the globe by the preoperative intravenous use of Diamox (500 mg., one hour before surgery) and by digital pressure (Chandler,² Kirsch

and Steinman,³ Gartner⁴) on the closed eyelids and orbit immediately following the retrobulbar injection (the latter maneuver has been used for over 30 years by me for a period of five minutes or longer for the prevention of possible retrobulbar hemorrhage and for globe softening), (6) avoidance of accidental pressure or traction on the globe by instruments, fingers, or sutures, (7) the use of hard tissue appositional sutures for closing the incision, and (8) stolid calmness in surgeon and patient.

To the above, enzymatic zonulolysis, may now be added for the purpose of diminishing the effect of the combined forces of traction and pressure necessary to rupture a relatively tough zonule and thus avoid zonular transmitted traction to the ciliary body, vitreous, and retina. This should probably lessen the likelihood of early and late hemorrhage from one of the vascular structures, of traumatic cyclitis, and even the danger of retinal breaks and detachment.

Some questions present themselves in the consideration of the new procedure:

1. Is a zonulolytic adjuvant necessary or advisable?
2. In what type of case should it be used?
3. What is the nature of alpha chymotrypsin?
4. What concentrations give the optimum zonulolytic effect without damaging ocular tissue?
5. What commercial products are available? Do they differ?
6. What might inactivate the enzyme and limit its effects?
7. Does it complicate the lens extraction in any way?
8. What complications have occurred or are prone to occur?
9. Is there any apparent damage to the ocular structures?

* Presented at the 95th annual meeting of the American Ophthalmological Society, Hot Springs, Virginia, May, 1959. The term "zonulolysis enzymatica" was introduced by Joaquín Barraquer in April, 1958, when he first reported the use of alpha chymotrypsin in cataract surgery. Alpha Chymar[®] was courteously supplied to me by Dr. J. Hubata and Mr. C. Damaskus of Armour Pharmaceutical Company, Kankakee, Illinois. It has been released for regular clinical use. Quimotrase[®], P.E.V.Y.A. Laboratories, Barcelona, was kindly sent to me by my former house officer, Dr. Manuel Diaz of Valencia, Spain.

10. Is the convalescence complicated in any way?

11. Are there contradictions to the use of chymotrypsin?

12. What happens to the zonula following chymotrypsin use?

13. Above all, is the use of alpha chymotrypsin safe?

It is obvious from a preceding paragraph that there are categorical advantages to the use of a relatively innocuous zonulolytic agent in cataract surgery if such an agent has become available. An understanding of zonular anatomy is helpful in connection with the new technique.

THE ZONULA

Both McCulloch⁵ and Vail,⁶ in exhaustive contributions on the zonula, the former in his thesis for the American Ophthalmological Society and the latter in his Doyné Memorial Lecture to the 1957 Oxford Ophthalmological Congress, confirmed the intimate zonular fiber attachment (1) to the pars plana ciliaris near the ora serrata, (2) to the vitreous near its base and (3) to the retina in the spikes of the ora serrata. They agree to the presence of Petit's and Hannover's canals. The former lies between the posterior zonular leaf and the anterior hyaloid and the latter between the anterior and posterior zonular leaves and the equatorial lens capsule. Vail⁶ confirmed anatomically the presence of Wieger's ligamentum hyaloideocapsulare. An extensive bibliography is incorporated in each of the above articles. (The position of the anatomic structures mentioned above can be seen in Figure 1.) A careful review of these two papers is invaluable for a proper concept of lens-zonule relationships in cataract surgery and for logical and safe management of lens delivery with the aid of enzymatic zonulolysis.

Minsky's^{28,29} and Goldsmith's³⁰ studies in zonular anatomy deserve careful perusal.

NATURE OF ALPHA CHYMOTRYPSIN

Alpha chymotrypsin is a proteolytic en-

zyme extracted from bovine pancreas in the inactive crystalline precursor form of chymotrypsinogen. It is transformed to the active form, alpha chymotrypsin, by the action of trypsin. The inactive precursor and the active crystalline form of chymotrypsin were first isolated in 1935 by Kunitz and Northrop.⁷ The extracted material is purified, lyophilized, and recrystallized several times by the method of Kunitz to form the product which is used in cataract surgery. It derives its name "chymo"-trypsin from its curdling effect on milk. Trypsin, which resembles it, does not generally curdle milk. A.C.T. further differs from trypsin in that the latter clots blood, while alpha chymotrypsin does not have a blood-clotting effect and that its action as an endopeptidase cleaves different portions of the protein molecule. It may also act as an exopeptidase.

Chymotrypsin can exist in several forms: alpha, beta, gamma, delta, epsilon, and pi. There is an unrelated chymotrypsin B and an alpha chymotrypsin dimer. Alpha chymotrypsin appears to be the best suited form for ocular surgery.

AVAILABLE ALPHA CHYMOTRYPSIN PRODUCTS*

Alpha chymotrypsin is available in the United States as Alpha Chymar,[®] produced by Armour Pharmaceutical Company and as Quimotrase,[®] made by P.E.V.Y.A. Laboratories of Barcelona. It is available in Great Britain as the original Spanish product, Quimotrase,[®] as the South African product, Zonulysin,[®] as the British Armour product termed Chymarzon.[®] There are a number of proteolytic drugs available for general surgical and medical use which are not applicable for enzymatic zonulolysis.

ASSAY CONTROL OF PROTEOLYTIC ACTIVITY

The proteolytic activity of alpha chymotrypsin is determined in this country chiefly by a modification of Anson's hemoglobin

* Zolyse[®] recently marketed by Alcon, Fort Worth, Texas, is Armour's Alpha Chymar[®] supplied with a special diluent.

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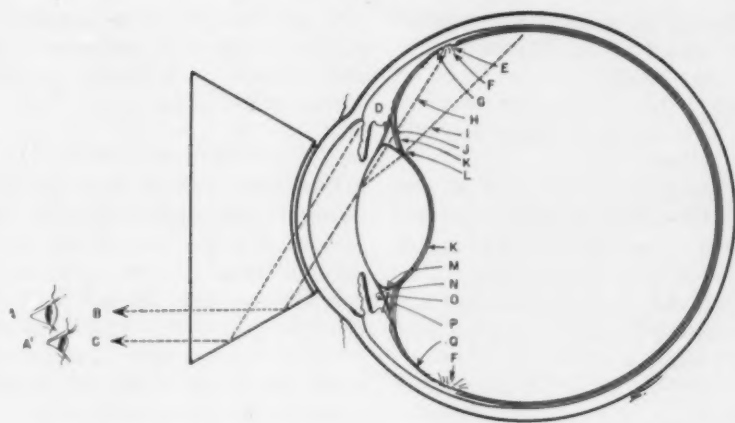


Fig. 1 (Thorpe). Diagram of anteroposterior section of human eyeball showing the path of light beams during goniocycloscopy and peripheral ophthalmoscopy with the Allen-Thorpe gonioprism in a phakic and an aphakic eye.

- A, A'—Observer
- B—Light beam from the interior ocular periphery (being continuous with line H in aphakia, or with light beam I when the crystalline lens is in situ)
- C—Gonioscopic light beam from iridocorneal angle
- D—Corpus ciliaris
- E—Ora serrata
- F—Vitreous base
- G—Region of zonular fibre attachment to pars plana ciliaris
- H—Light beam in aphakia, from extreme periphery continuous with B
- I—Light beam, continuation B, in the phakic eye
- J—Posterior zonular leaf
- K—Anterior hyaloid
- L—Wieger's (hyaloideocapsular) ligament
- M—Equator of crystalline lens
- N—Anterior zonular leaf
- O—Hannover's canal (perilental space between anterior and posterior zonular leaves)
- P—Petit's space between posterior zonular leaf and anterior hyaloid
- Q—Posterior insertion of zonular fibers

Note: The observed zones covered by the light beams BH and BI can be increased either by slight upward or downward rotation of the eyeball, or by shifting the gonioprism slightly on the corneal surface in the corresponding direction.

assay method in terms of "Armour units of proteolytic activity," or preferably "APAu" for abbreviation of APA units. One hemoglobin unit under the standard assay conditions of Anson represents the amount of enzyme which releases one microgram of tyrosine from denatured hemoglobin substrate. The solid crystallized substance may vary somewhat in its proteolytic activity when prepared by different laboratories (possibly due to water of crystallization or to the presence of inactive content). It is obviously important to have an accurate assay of the

proteolytic activity of the material employed for zonulolysis.

OPTIMUM DILUTION OF ALPHA CHYMOTRYPSIN

Quimotrase® is used for enzymatic zonulolysis in 1:500 dilution. Two milligrams of the crystalline solid substance, the contents of one ampule, as supplied for clinical use by P.E.V.Y.A., are dissolved in 10 cc. of sterile physiologic saline to make a 1:5000 dilution for clinical use. The crystalline Quimotrase® material assays average at 750

APA units/mg. This equals 150 APA units/cc. of the prepared clinical dilution.

Thus:

$$\frac{2 \text{ mg.} \times 750 \text{ u.}}{10 \text{ cc.}} = 150 \text{ u./cc. for product "Q"}$$

(where "u" stands for APA units). Crystalline Alpha Chymar® assays average at 1150 APA units/mg. One ampule contains 0.652 \pm mg. of the drug. To this is added 5.0 cc. of sterile physiologic saline. The result is a solution containing 750 APA units in 5.0 cc. or 150 APA units/cc.

Thus:

$$\frac{0.652 \text{ mg.} \times 1150 \text{ u.}}{5 \text{ cc.}} =$$

150 u./cc. for product "A"

Dissolving the crystalline solid contained in an Alpha Chymar® vial in 5.0 cc. of physiologic saline results in a solution which is the proteolytic equivalent of a 1:5000 dilution of Quimotrase®.

The optimum dilution for zonulolysis in human cataract surgery was confirmed by our tests to be 150 APAu./cc. Alpha Chymar® and Quimotrase® at 150 APA units/cc. have identical zonulolytic effects.

Curiously, the above materials have proven to be rather inadequate for zonulolysis in slaughterhouse eyes in the above concentration.

ENZYME INHIBITION AND INACTIVATION

Although α -chymotrypsin is stable when properly cared for, its enzymatic action may be inactivated or inhibited by a number of conditions according to the manufacturer's report. Among these are: storage in hot areas; contact of the diluted mixture with alcohol; more than a six-hour open-exposure of prepared mixture at room temperature; contact with soaps, detergents, strong alkalis, strong acids, and some antiseptics. Its potency is not affected by penicillin, tetracycline or dihydrostreptomycin. The dissolved material should therefore be prepared for use in sterile, chemically clean, containers and syringes.

Dry medicine glasses or metal containers may have a residue of detergents or alkali on their surfaces. This must be removed with sterile distilled water.

SURVEY OF LITERATURE

The literature on the use of alpha chymotrypsin for intracapsular cataract surgery is growing. Shortly after Barraquer's¹ communication, case reports appeared by Cogan,² Moffat and Pierse,³ Inouye,¹⁰ Malbran,¹¹ and Remky.¹² Vail,¹³ Newell,¹⁴ and Troutman¹⁵ commented on enzymatic zonulolysis editorially. At the 18th International Congress in September, 1958, considerable interest was attracted to the subject.

The American Academy of Ophthalmology and Otolaryngology set up a central committee with Troutman as co-ordinator for alpha chymotrypsin. Both Barraquer's and Ferrer's¹⁶ motion picture films of enzymatic zonulolysis were shown at the October, 1958, Academy meeting.

Rizzuti¹⁷ published the first series of case reports in the American ophthalmic literature. Thorpe¹⁸ reported his experiences with alpha chymotrypsin at the Florida University midwinter seminar in February, 1959. Fassanella¹⁹ discussed his personal experiences with me and reported considerable pigment scattering at surgery after use of the enzyme. But he had no untoward complications. Recently, Cogan, Simons, and Gibbs,²⁰ Ainslie,²¹ and Zorab²² published their experiences.

Many ophthalmologists are using the new procedure. The general comment on the use of alpha chymotrypsin for zonulolysis by the reporting surgeons is extremely favorable. A few men ran into occasional complications. Many surgeons^{13, 15, 18} preferred not to use the material in infants or children with congenital cataract.

PREPARATION AND SURGICAL TECHNIQUE

Patients for cataract surgery were admitted to the hospital on the day before surgery after ascertaining previously their

health status by history, physical, and laboratory examinations. Inquiry was made about allergies and drug sensitivity. Tear duct patency, a negative conjunctival smear, absence of respiratory or other infections and diabetes control were prerequisites. Pre-admission tests for the particular barbiturate to be used were done. A 0.5-percent chloramphenicol solution was instilled in the conjunctival sac for several days before surgery.

The pupil of the eye to be operated was dilated with 10-percent Neosynephrine and two-percent Homatropine and Diamox (500 mg.) was given intravenously one hour before surgery. The usual precautionary measures included: sedation, facial nerve block for orbicularis akinesia, topical instillation of tetracain and 1:1000 adrenalin, retrobulbar procain-hyaluronidase-adrenalin injection, and subconjunctival procain-cocain-adrenalin injection at the lower limbus for maximal downward pupil dilatation, procain injection of the superior rectus tendon, a routine superior rectus bridle suture and a lateral canthotomy when necessary.

The surgery consisted of the following steps (figs. 2, 3, and 4).

1. A three-mm. wide limbus-based flap was prepared.

2. A scleral groove was cut 1.5 mm. from the upper limbus, concentric with it and extending from the 9- to 3-o'clock positions.

3. Five scleral appositional sutures were placed.

4. A keratome incision was made between the 9- and 10-o'clock positions (fig. 2-B) inside the scleral groove.

5. The anterior chamber was filled with air to expel all aqueous and to deepen the chamber. The incision was readily completed from right to left with Castroviejo's angled corneal scissors and Westcott's spring scissors.

6. Enzyme instillation: 0.25 to 0.3 cc. alpha chymotrypsin solution was gently injected beneath the iris pupil border with a small syringe and a blunt smooth No. 27-gauge cannula (fig. 3), being careful to

avoid iris prolapse. (The normal aqueous volume amounts to 0.15 cc. The volume of the posterior chamber is one-fourth of that.) When iris prolapse occurred, it was replaced with an iris repositor.

7. (a) One or two peripheral iridectomies were performed above while waiting for the enzyme to work. (In some cases, the enzyme was injected through the peripheral iridectomy (fig. 4) or through the iris coloboma after completion of the iris surgery.) (b) A basal full-sector iridectomy was performed in cases of glaucoma, previous uveitis with posterior synechia, or previous retinal detachment.

8. Enzyme irrigation. The anterior and posterior chambers were gently washed with one to two cc. of physiologic saline. An empirical waiting period was established for various ages. Two minutes for patients over 60 years of age, 2.5 minutes for patients between 50 and 60, and three minutes for patients between 30 and 50. Irrigation was performed at the end of four minutes in patients under 30 years of age. If the presence of a tough zonule was suspected in patients over 30 years, the waiting period was set at between three and three and one-half minutes. The reasoning was to allow a longer period for the enzyme to work in younger patients and in tougher zonules.*

9. The lid speculum was now held up one mm. from the eyeball by an assistant if this was deemed to be necessary. Adrenalin was instilled if the pupil had contracted.

10. The lens capsule was grasped and delivered with the erisophake or Arruga forceps with external counter-pressure (step 12). My preference now is for the capsule forceps except in intumescent cataracts or distended capsules.

11. The lens was either tumbled or slid out, by the Verhoeff technique which the late Dr. Kirby favored so much. The latter was

*Note: In some cases, enzyme injection was performed just following the air instillation (in Step 5 above). The injection was completed immediately thereafter.

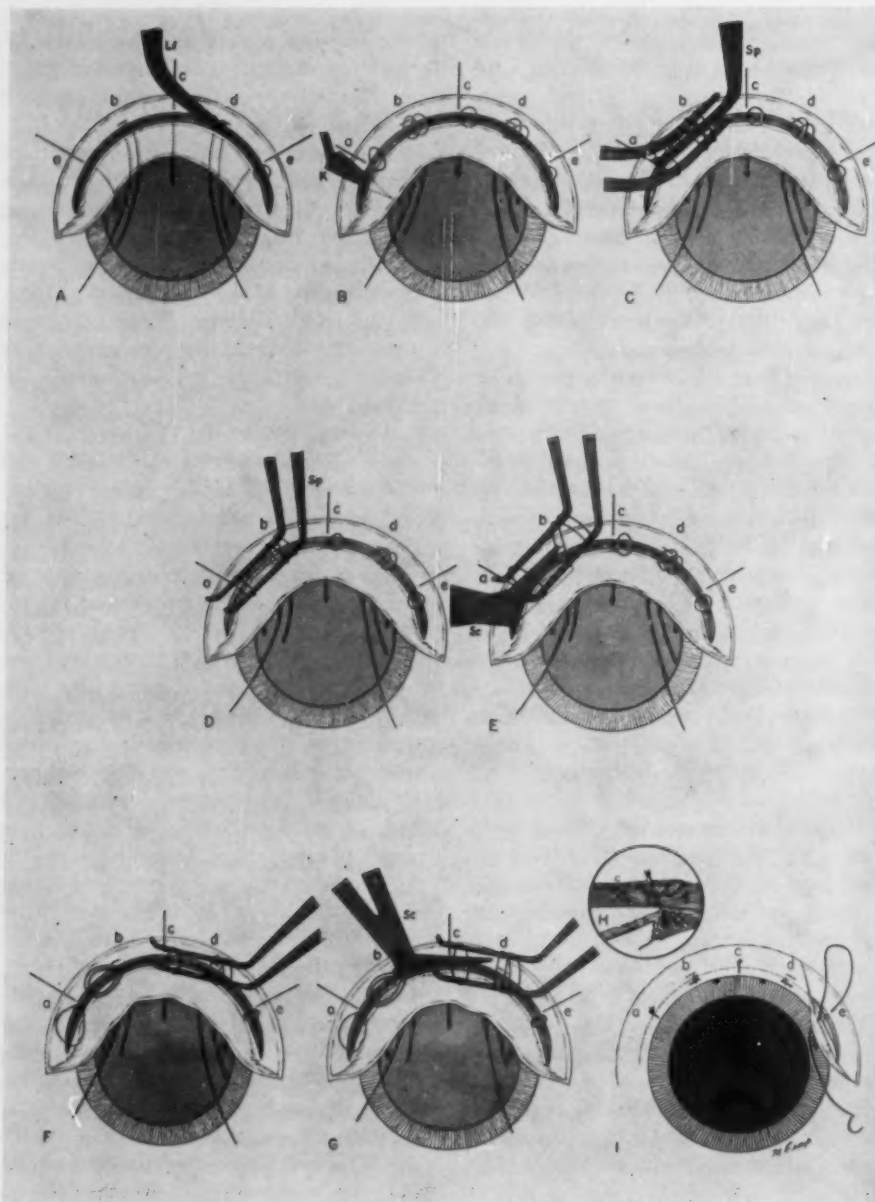
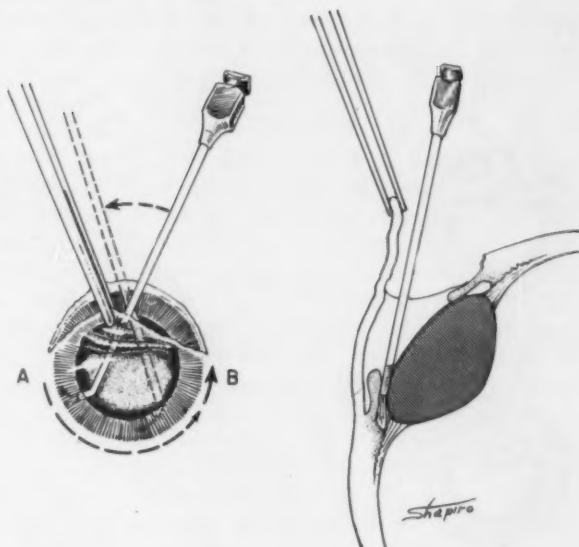


Fig. 2 (Thorpe). Diagram of keratome-scissors incision technique (five preplaced appositional 6-0 silk sutures).

A. Scleral groove extends from the 9- to 3-o'clock meridian, 1.5 mm. behind limbus; b,d, mattress appositional sutures at the 11- and 1-o'clock meridians are passed first through posterior lip of incision, radially across trough of groove through anterior lip, and through the limbus-based conjunctival flap c; a,c,e, interrupted sutures, McLean type, placed radially like b and d, thread knotted on corneal side.

Fig. 3 (Thorpe). Technique of enzyme instillation into the posterior aqueous chamber beneath the dilated pupil margin.

Arrow AB—Backward sweep of smooth cannula knee as the enzyme is being injected into the posterior chamber.



done in 20 percent of the cases (in the presence of a large diameter lens). The Bell or Harrington erisophake was used in the first 40 cases. The capsule forceps was employed regularly in the next 37 cases except for intumescent cataracts or for those cases in which the forceps slipped off on attempt at grasping the lens.

12. Counter-pressure was made at the inferior limbus and followed upward with a round tipped muscle hook. This served to tuck the cornea beneath the tumbling lens or to wedge the sliding lens against the upper wound margin as it was emerging therefrom. The enzymatic zonulolysis permits the lens to come forward and often makes the deliv-

ery so easy that the surgeon is prone to slide or lift the lens out without the follow-up of the cornea tucked against it. The corneal tuck maneuver overcomes such carelessness and will usually prevent vitreous loss in cases of firm attachment between Wieger's ligament, the hyaloid and the lens. It is an important maneuver (Vail⁶ stresses this point). I believe it succeeds in breaking and wiping Wieger's ligament from the posterior lens capsule and thus avoids drag on the vitreous. (Vitreous expulsion is likely to occur in cases with increased vitreous chamber pressure or with incomplete akinesia and especially in the presence of a stout hyaloid-capsular attachment even if the eye is very soft.)

Lf, looping-out forceps, brings silk thread out of groove. Loops are draped to patient's left.

B. K, narrow keratome, makes three to four-mm. wide incision into anterior chamber at the 9-o'clock meridian through deepest portion of groove. Loops, a,b,c,d,e, are draped on sclera to patient's left.

C. Forceps Lf acts as guide in draping suture loops a and b onto Sp, suture spreading forceps.

D. Sutures a and b draped on forceps Sp, preparatory to entry of anterior chamber with scissors.

E. Sc, angled Castroviejo corneal spring scissors cuts between threads of loops a and b which are spread open by Sp. Scissors incision is carried almost to the 12-o'clock meridian.

F. Sutures c and d are draped on spreading forceps.

G. Scissors incision is carried between threads of opposite lips up to suture, e. Incision is completed with aid of spreading forceps past suture, e, to the 3-o'clock meridian.

H. (inset). Sectional view of scleral incision and mattress suture: C = cornea, S = sclera.

I. After preliminary iridectomy, cataract extraction, and toilet of wound. Manner of passing upper end of interrupted suture through conjunctiva preliminary to tying knot of suture e is shown. Sutures b and d were first. Then sutures a and c were tied before turning to e.

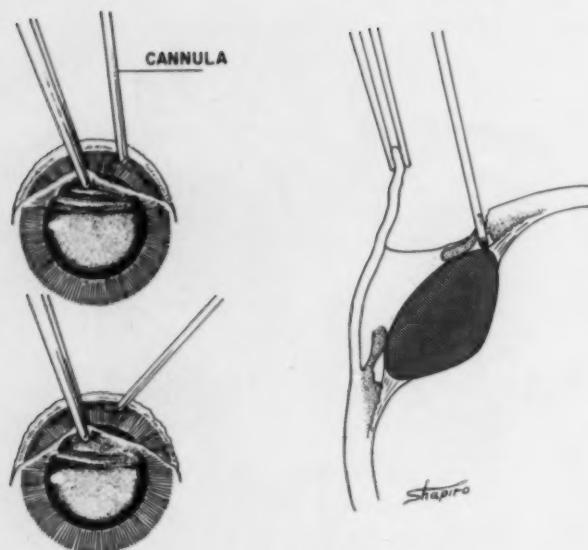


Fig. 4 (Thorpe). Alternate technique of enzyme instillation into posterior chamber through orifice of peripheral iridectomy. It is done both nasally and temporally and is combined with the technique shown in Figure 3.

13. The corneal lip was now stroked into proper position with the extracted lens surface and the 12-o'clock suture was pulled up simultaneously. The iris was allowed to resume its normal position.

14. Toilet of the wound was performed.

15. The other sutures were now gently pulled up.

16. The scleral sutures bridging the incision were now tied. Note: 6-0 silk was used as a suture material in 90 percent of the cases. The five silk scleral sutures were preplaced. When 6-0 chronic catgut was used, three of these sutures (fig. 2-b, c, d,) were preplaced and the rest were postplaced. The catgut sutures did not penetrate the conjunctiva. The conjunctiva was closed over the catgut sutures.

17. An air bubble was now instilled into the anterior chamber.

18. Pilocarpine was now dropped in the eye in an occasional round pupil case. Atropine (two percent) was routinely instilled when a full-sector basal iridectomy had been performed.

19. The conjunctival incision was closed by a running appositional conjunctival suture.

20. A subconjunctival injection of 1,000 to 2,000 units of penicillin contained in 0.25 cc. of solution was given in the lower conjunctiva in nonsensitive cases.

21. Both eyes were occluded with separate eyepad dressings. A metal protective shield was placed on the operated eye. The patient was given a back rest, allowed a sip of water, and sent back to his room.

POSTOPERATIVE CARE

The dressing was removed from the unoperated eye three hours after surgery and the patient was permitted out of bed on a chair at that time. The operated eye was dressed 48 hours after surgery and two to four-percent atropine was usually instilled. Daily dressings were done.

Both eyes were left open on the eighth postoperative day. The conjunctival suture was removed on the eighth day. The patient was sent home eight to 10 days postoperatively. The silk scleral sutures were allowed to stay in for three weeks; and if they appeared buried, an extra week was allowed to pass before removal. On rare occasions, the silk sutures were removed at the end of two weeks.

At each dressing one noted the following: (1) extent of inflammation, (2) condition of the cornea, (3) depth of the anterior chamber, (4) position and dilatation of the pupil, (5) position and size of the air bubble (in rare instances, the bubble was behind the iris—maximal dilatation of the pupil with atropine, Cyclogyl, and Neosynephrine [10 per cent] while the patient was kept flat on his back, caused the bubble to come forward in all instances), (6) the position of the conjunctival suture, and (7) the presence of hemorrhage or exudate.

The convalescent period after discharge from the hospital, was marked by weekly or fortnightly inspection, fundus and slitlamp examination. Preliminary refraction was done at the first or second, convalescent period, office visit. Slitlamp gonioscopy was performed about six weeks after surgery. This procedure proved very informative to me in a previous study²³ of 318 consecutive cataract operations. It gave information on (1) the incisional healing at the endothelial inner side of the wound, (2) the presence and character of peripheral anterior synechia, (3) the status of the hyaloid, (4) the intact presence of the complete zonular membrane with its foramenlike round orifice, (5) the status of the corneal endothelium, (6) the condition of the ciliary processes (which were visible only in sector iridectomy cases), and (7) the pars plana, vitreous base, anterior and posterior hyaloid, and on the peripheral retina. The best gonioscopic examinations were made in the presence of a dilated pupil or a sector iridectomy.

Allen, Braley, and Thorpe²⁴ have pointed out the readiness with which the four mirror gonioscopes can be used for gonioscopy as well as for examination of the lens equatorial region, the ciliary body, and the peripheral retina. I^{25, 26} reported further on these techniques with the use of the Allen-Thorpe gonioscopes. Burian and Allen²⁷ gave an excellent illustrated report on the mechanical changes of the structures lying near the lens equator during accommodation as observed by gonioscopy. They noted the move-

ments of the peripheral anterior hyaloid, variations in dimension of Petit's space, and Wieger's ligament among other things.

SELECTION OF CASES

The reported series includes 71 private cases operated by me and six cases operated by my senior ophthalmic resident, Dr. N. Mittica, at Montefiore Hospital. The patients varied between 18 and 83 years of age. Preference for enzyme use was originally planned for patients under 50 but was finally accorded to (1) patients under 60 years of age, (2) high myopes, (3) diabetics and others with likelihood of ciliary or retinal hemorrhage, (4) intumescent cataract cases, (5) previous iridocyclitis cases, (6) complicated cataracts, (7) glaucoma with cataracts, (8) in previously cured retinal detachments, and (9) those instances where a tough zonule or fragile capsule was encountered at attempted lens removal or found at previous surgery on the fellow eye. However, some cases were included in the reported series which did not fall into the above groupings, because of the surgeon's desire to create a broader base of experience (table 1).

Concurrently, a smaller series of cataract cases (not included in this report) were operated without the use of alpha chymotrypsin. They were primarily (1) patients over 65 years of age with previous uneventful cataract surgery (easily broken zonular ligaments), (2) patients with tremulous iris or preoperative slitlamp evidence of vitreous hernia into the anterior chamber, (3) cases

TABLE 1
AGE DISTRIBUTION OF 77 PATIENTS OPERATED WITH
THE AID OF ALPHA CHYMOTRYPSIN

Ages (yr.)	No. of Cases
1-10	0
11-20	1
21-30	0
31-40	4
41-50	8
51-60	15
61-70	32
71-80	15
81-90	2
TOTAL	77

presenting endothelial dystrophy or mild Fuchs' epithelial dystrophy and (4) patients under 16 years of age.

UNNECESSARY AND CONTRAINDICATED USE OF ALPHA CHYMOTRYPSIN

1. Thus in previously operated senile cataract patients with frail zonules, the use of alpha chymotrypsin in the fellow eye would seem unnecessary.

2. On the other hand, alpha chymotrypsin use would appear to be contraindicated in patients with tremulous iris and slitlamp evidence of vitreous hernia at the pupil margin. Alpha chymotrypsin use in the anterior chamber in the presence of a vitreous hernia might find that enzyme action on the intact portion of the zonula would be blocked by a layer of vitreous. The presence of a zonular defect might be followed by loss of the subluxated cataract into the vitreous depths.

3. Alpha chymotrypsin use would appear to be contraindicated in the presence of endothelial dystrophy for one would expect the enzyme to affect deleteriously the partly degenerated endothelium and thus aggravate the corneal process into a Fuchs' type of epithelial dystrophy.

The last contraindication (3) has so far been contradicted by events in a personally operated cataract case (E. R., aged 71 years). This patient had endothelial dystrophy with early epithelial changes. Alpha chymotrypsin was unintentionally and inadvertently used in this case without visible harmful effect. The convalescence was entirely uneventful. There was no corneal edema. The incision healed with a minimum of post-operative reaction. The visual acuity with prescribed refractive correction six weeks after surgery was 20/40+. Ophthalmoscopy reveals fine degenerative changes in the macular retina.

4. Alpha chymotrypsin use appears to be contraindicated in patients under 16 years of age—because the firm hyaloideocapsular attachment leads to vitreous prolapse.

OBSERVATIONS DURING CATARACT SURGERY WITH ALPHA CHYMOTRYPSIN

EASE OF ZONULAR SEPARATION

The zonula separated from the lens capsule with marked ease in all instances, in which the period of time for enzyme action in the posterior chamber (before saline irrigation) was two or three minutes and, in which the concentration of enzyme employed was 100 to 150 APA u./cc. (These concentrations as stated above were respectively equivalent to a 1:7,500 to 1:5,000 dilution of Quimotrase®.)

In 49 cases of the 77 operations with alpha chymotrypsin enzyme, the zonula appeared to have completely given up its attachment to the lens, so that no portion of the zonula could be seen attached to the upper lens equator at the time of extraction. Among these were three patients who sometime previously had an "unintentional" extracapsular extraction performed on the fellow eye. In 25 additional cases, the upper zonula was visualized at the time of the lens extraction, but it separated from the lens equator with ease and without additional manipulation.

FAILURE OF ZONULOLYTIC EFFECT

In three cases, which were operated on two different operating sessions employing fresh preparations of alpha chymotrypsin at each session, no enzymatic zonulolysis seemed to take place. Two of these cases (mother and son), were operated on the same morning. The same preparation of alpha chymotrypsin (150 APA units/cc.), for a three-minute period, was used for both. Enzymatic zonulolysis failed to take place.

E.R., aged 32 years, a myope of 7.0 diopters, with bilateral advanced cataracts, had a capsule rupture on attempt at forceps intracapsular extraction through a large round pupil. Three minutes had been allowed to pass after 0.25 cc. alpha chymotrypsin was instilled beneath the iris, before the enzyme was washed away. The opera-

tion resulted in an extracapsular extraction which was otherwise uneventful. He had a good convalescence. Visual acuity six weeks after surgery was 20/30—with a corrective lens.

S.R., aged 64 years, with senile cataracts, mother of the above patient, was operated the same morning, using the same preparation of alpha chymotrypsin. No demonstrable zonulolytic effect was obtained from the subiridic instillation of 0.3 cc. alpha chymotrypsin solution in concentration of 150 APA units/cc. for an action period of three full minutes. A regular round pupil intracapsular forceps extraction was performed. The patient had a tough zonula.

The circumstances of surgery in the previous two cases were later reviewed. A new technician-aide in the operating room had prepared the alpha chymotrypsin dilution, on this occasion, in an open medicine glass which may have had some alkali in it. A wet syringe, which had been removed from an alcohol solution, was used to take up the diluent saline instead of a dry syringe. A bottle of alpha chymotrypsin from the same batch of enzyme was retested and found to have full proteolytic activity. It was concluded that the alpha chymotrypsin solution had apparently been inactivated by improper preparation without the surgeon's knowledge.

It is important that a chemically clean dry sterile syringe be used to make up the dilution and that the dissolved material remain in the special No. 1 type glass container supplied by the manufacturer. It is made of practically alkali nonleeching glass.

Active alpha chymotrypsin was found ineffective in an 18-year-old patient. J. W., with traumatic cataract, was operated at another operating session, on another day, than the two patients on whom the alpha chymotrypsin zonulolysis attempts had failed. The proteolytic activity of the alpha chymotrypsin preparation was not in question, for it had proven to be potent earlier

that morning. The enzyme was allowed to act for fully three minutes before being washed away. An Arruga capsule forceps was used to grasp the capsule and only succeeded in tearing away a large portion of the anterior capsule. The relatively soft lens material was removed by simple extracapsular extraction. An unsuccessful attempt was made to tease out the remaining capsule. One could observe the intact zonular membrane but the capsule would not separate from the zonula. It was decided not to risk vitreous loss and let the eye well enough alone. The patient recovered from his extracapsular extraction and now has 20/25 vision with an aphakic correction. The three-minute period of active enzyme action was evidently inadequate for the material to produce zonulolysis in this patient. There are two possible reasons for this. Three minutes is too short a period for adequate enzyme action in a young person with a tough zonule. The possible organization of a fine layer of exudate into connective tissue on the zonular surface may have prevented zonulolysis.

It was also noted that posterior synechia in cases of former uveitis had to be separated mechanically before cataract extraction. In a similar previous case, the enzyme failed to lyse posterior iris synechia. I then decided to break posterior iris synechia mechanically before instilling alpha chymotrypsin.

COMPLICATIONS DURING SURGERY

Very few complications occurred during surgery in this series of 77 cases. There was one case of vitreous loss, a case of hyaloid presentation without prolapse, five cases of capsule rupture, and 11 cases of erisophake slippage.

VITREOUS PROLAPSE (one case)

The vitreous prolapse occurred in a Verhoeff lens extraction sliding procedure with forceps. The lens seemed adherent to the posterior lens capsule. The case of vitreous

presentation without prolapse, occurred in a tumbling procedure with the Bell erisophake. Both of the above were probably due to one, or both, of two factors (1) a stout hyaloideo-capsular ligament, or (2) strong negative pressure holding the lens against the patellar fossa of the hyaloid (a sort of suction phenomenon.) In neither instance was there a follow-through by the muscle hook for tucking the cornea against the lens. *The corneal tucking maneuver apparently serves to wipe the normal vitreous adherence from the posterior capsule.*

There is considerable temptation with the use of alpha chymotrypsin just to lift or slide the lens out. This is often quite easy to do. But the temptation should be guarded against and complications should be avoided by the above-mentioned maneuver.

CAPSULE RUPTURE (five cases)

There were five cases of capsule rupture. The first instance occurred in a patient in whom a weak test solution of alpha chymotrypsin (1:30,000 dilution-25 APA u/cc.), was employed. This was during the period of potency evaluation. An erisophake had slipped off after the lens was in the process of delivery. A capsule forceps was then applied and resulted in prompt capsule rupture. The result was an extracapsular extraction. The effect of the enzyme on the zonule was apparently negligible in this case. Only part of the capsule could be removed. Two cases of capsule rupture occurred when an excessive vacuum was applied by the erisophake. The capsules were successfully teased out with forceps after the lens nucleus was expressed. The cortical material was readily irrigated. Enzymatic zonulolysis had evidently taken place.

Another case was that of the 32-year-old person already mentioned in whom inactivated enzyme material was used. The fifth case of capsule rupture was that of J. W., the 18-year-old patient with traumatic cataract in whom zonulolysis failed to take place.

ERISOPHAKES SLIPPAGE NEGLIGIBLE (11 cases)

The erisophake slipped off in 11 cases and was reapplied once or twice in each instance with completion of the intracapsular extraction. It proved to be insignificant.

IRIS PROLAPSE DURING SURGERY (two cases)

In two instances, iris prolapse occurred during injection of alpha chymotrypsin solution into the posterior chamber. This was readily replaced with the iris spatula and the operation was completed in the usual manner.

No other complications occurred during the surgery.

POSTOPERATIVE COMPLICATIONS

I abandoned corneal incisions and corneal sutures in favor of a scleral incision and preplaced scleral sutures, in cataract surgery, more than a decade ago, with the following in mind: (1) to reduce the incidence of striate keratitis, which I felt was due to corneal trauma of the scissors incision, plus the continuous wick-action of suture material in the corneal stroma, and (2) for the purpose of preventing the aggravation of an endothelial or mild epithelial dystrophy, into a full-blown epithelial dystrophy. Nearly all extractions were done with capsule forceps.

The passage of time justified this assumption for striate keratitis and aggravation of corneal dystrophy became rather infrequent occurrences in the presence of a scleral groove incision closed by scleral sutures. However, in this series, the old devil reared his head again.

POSTOPERATIVE TRANSIENT FOLDS IN DESCMET'S MEMBRANE (KERATITIS STRIATA)

A. *Erisophake used in 40 cases.* The first 40 cataract extractions in the alpha chymotrypsin series were operated with the erisophake. One of these cases was partially completed with forceps. There was a relatively high incidence of folds in Descemet's

membrane during the immediate postoperative period in this group. These amounted to 24 cases or 60 percent of the 40 erisophake extracted cases. The folds usually cleared within the first two weeks after surgery. One case of polycythemia with cataract, in which the enzyme was used, developed a flat chamber on the eighth postoperative day due to a suture leak. The striate keratitis which developed, failed to clear completely, even, after suture removal, although the wound leak had been repaired and the anterior chamber had long been reformed. There was no vitreous corneal adhesion. Final visual acuity was 20/70.

B. Capsule forceps preferred. The shift was made to capsule forceps extraction due to the high incidence of Descemet's membrane folds in the immediate postoperative period of the erisophake extractions with alpha chymotrypsin. Three patients operated with alpha chymotrypsin and capsule forceps, out of 37 developed a few small folds in Descemet's membrane. These cleared within a week after surgery.

One must therefore conclude that the use of a relatively bulky erisophake cup in the anterior chamber probably caused a temporary traumatic disturbance of the corneal endothelium resulting in secondary corneal edema and folds in Descemet's membrane.

Capsule forceps was, previous to alpha chymotrypsin use, my routine procedure. It is now, also, preferred for extraction in alpha chymotrypsin cases.

UVEITIS (TRANSIENT)

There were no cases of severe uveitis in the postoperative period. The average length of time for the operated eye to become totally white was 41 days in the alpha chymotrypsin erisophake series. This was about eight days longer than previous comparative experience. There was a mildly positive aqueous flare with formed elements.

The alpha chymotrypsin group of cases in which capsule forceps was employed for lens

extraction averaged 29+ days of hyperemia. (In both groups, local steroid therapy was begun on the 14th postoperative day as a routine measure.) Some of the reaction was ascribable to the subconjunctival penicillin injection given on completion of surgery.

Alpha chymotrypsin was at first suspected to be the cause of mild uveitis. It was soon established that the eyes with vacuum cup extractions had a longer period of postoperative inflammation with a higher incidence of corneal edema than a similar group of forceps operated cases in the alpha chymotrypsin series. It was then concluded that the alpha chymotrypsin was not a related factor in prolonging the period of postoperative hyperemia. It is my impression that as our alpha chymotrypsin experience increases, there may be hope for a shortening of the postoperative inflammatory period. This can be hoped for on a basis of abolished zonulociliary traction in adequate enzymatic zonulolysis.

DISCUSSION

The visual results in this alpha chymotrypsin series matched the corrected acuity of previously operated nonenzyme cases. When the neurologic and perceptive mechanisms (macula, retina, optic nerve) were intact, and the media were clear, when there was no field defect, or previous amblyopia, now the vision improved, so as to match that of patients operated without alpha chymotrypsin. The postoperative corneal astigmatism was apparently not altered by the use of alpha chymotrypsin.

Alpha chymotrypsin used in surgery of the fellow eye in three patients with previous unintentional extracapsular senile cataract extractions resulted in full zonulolysis and easy cataract extraction. This was the opposite result of one instance in which an intracapsular operation was previously successful in one eye. In the fellow eye the above mentioned 1:30,000 dilution of alpha chymotrypsin was used, the vacuum cup dislodged the lens and then slipped off. Application of cap-

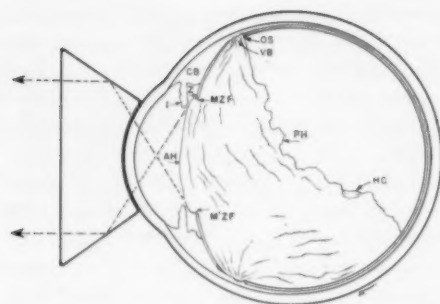


Fig. 5 (Thorpe). Diagram showing gonioscopic path of light rays in an anteroposterior section of an aphakic eye.

- ah—Anterior hyaloid
- i—Iris
- z—Attenuated zonular membrane
- mzf—Superior margin of zonular foramen in aphakia
- m'zf—Inferior margin of zonular foramen in aphakia
- os—Ora serrata
- vb—Vitreous base
- ph—Posterior hyaloid of collapsed vitreous in aphakia
- hc—Posterior orifice of hyaloid canal

sule forceps resulted in prompt capsule rupture and an extracapsular result. Alpha chymotrypsin may prove useful in facilitating removal of a thickened capsule remaining after unintentional extracapsular surgery. I have not attempted this as yet.

ZONULA AFTER INTRACAPSULAR CATARACT SURGERY (GONIOCYCLOSCOPY)

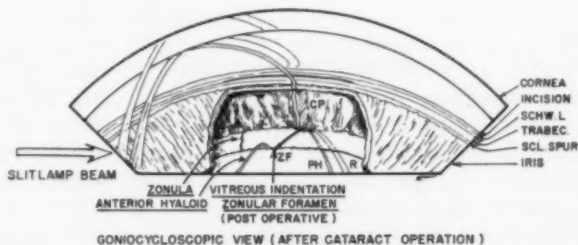
In a previously reported study,²³ I noted, on gonioscopic examination, the intact ap-

pearance of the zonular membrane after cataract surgery (fig. 5). One could also observe the vitreous hernia into the anterior chamber with the hyaloid indentation by the margin (fig. 5-MZF; fig. 6-ZF) of the aphakic "zonular foramen" (the site of the hyaloideocapsular ligament of Wieger). The vitreous hernia in the anterior chamber could be seen to pass through two orifices (1) the aphakic zonular foramen and (2) the pupil. One could also observe the ciliary processes, the pars plana, the base of the vitreous, the ora serrata, degenerative cystic and other changes in the peripheral retina and also the detached vitreous. This is an interesting and exciting view.

It became my conviction after an extension of the aforementioned study that the zonula was actually not torn during intracapsular surgery, but that it came away at its points of attachment at the capsular surface and retracted for a short distance behind the iris surface to remain an intact glasslike membrane with an open foramen or orifice, seven to eight mm. in diameter. This study was carried out during gonioscopy of healing cataract incisions, six or more weeks after surgery.

The method of examination can be gleaned from Figures 1 and 6. Each diagram portrays the path of light and the structures to be seen. (Figure 1 represents the phakic, and Figure 5 shows the aphakic eye.) Many of the structures which are normally hidden

Fig. 6 (Thorpe). View of superior angle after combined intracapsular cataract extraction with alpha chymotrypsin showing attenuated zonule of Zinn and slitlamp beam on ciliary body, herniating vitreous, and zonula. (See also Fig. 5.) Note: Continuous course of slitlamp beam as it outlines the anterior hyaloid, which is indented by the margin of the zonular foramen (ZF, MZF, M'ZF), and passes onto the zonular surface and then turns downward to outline the detached posterior hyaloid (PH), and the peripheral retinal surface (R).



from view by the iris can be seen in the presence of a sector coloboma and with a maximally dilated pupil.²⁴⁻²⁶ On occasion, one can see the broken-off ends of some zonular fibers in the ciliary valleys. The zonula can be seen gonioscopically after the usual intracapsular extraction to be a circular partly hemispherical membrane interposed between the hyaloid and the ciliary body and iris.

ZONULA IN INTRACAPSULAR CATARACT SURGERY AFTER USE OF ALPHA CHYMOTRYPSIN

Goniocycloscopy of the aphakic eye, six or more weeks after intracapsular surgery with the aid of alpha chymotrypsin, revealed the zonula, with a normal aphakic zonular orifice (aphakic "zonular foramen"), to be present in all of the 52 instances examined. In the patient with vitreous prolapse, already mentioned, the upper margin of the foramen was bent forward like a piece of cellophane. The zonular membrane appears somewhat grayish and etched after exposure to alpha chymotrypsin during surgery. The margin of the zonular foramen appears somewhat irregular in these cases (fig. 6). But the zonula, the vitreous hernial indentation, and the intact anterior hyaloid were readily visible.

Biomicroscopy of the inner eye in the retroiridic space thus revealed that the zonula was not dissolved but appeared slightly thinner in substance than usual.

EFFECTIVE SITE OF ALPHA CHYMOTRYPSIN ACTION

The irregularity of the zonular foramen margin caused me to conclude that the effective site of alpha chymotrypsin action in cataract surgery was the zonular attachment to the lens. This action seems to be rather specific for the 100-150 APau./cc. of alpha chymotrypsin and the three-minute period of enzymatic action. It may at times not reach Wieger's ligament which may explain the disasters of intracapsular surgery attempted in congenital cataracts of very young patients. (It will be noted that no

congenital cataracts appear in this series. None were attempted.)

WOUND HEALING

The previously mentioned gonioscopic study²³ of wound healing in 316 keratome and scissors incisions, showed the presence of a small cleft between the deep corneal wound margins in 21 percent of cases two months after surgery, while 76 percent appeared fully healed. In nearly two-thirds of this open percentage, the remaining cleft closed completely in another month.

This series of 77 alpha chymotrypsin cases is too small to arrive at final conclusions but of gonioscopy done in 52 of 71 private cases by me, 15 or 28.8 percent showed the presence of a small cleft between the wound margins on the endothelial side of the cornea, at the end of two months. Within another month, nine of these had closed. These cases are still being observed. The posterior wound hiatus may indicate a slight delay in wound healing, but the small number is inconclusive. It is probably in line with Barraquer's experience of three cases of late wound rupture, quoted by Troutman.¹⁵

PAIN ON ZONULAR TRACTION RELIEVED BY ALPHA CHYMOTRYPSIN ZONULOLYSIS

An attempt was made to do an intracapsular cataract extraction without enzyme on two patients, aged 68 and 72 years, respectively. They complained of pain when traction was made on the zonula. The forceps hold was released and alpha chymotrypsin was instilled. The cataracts were extracted without any manifestation of pain after the enzymatic zonulolysis took place.

SUMMARY AND CONCLUSIONS

Seventy-seven cataract extractions in patients between the ages of 18 and 83 years who were operated with the aid of alpha chymotrypsin for enzymatic zonulolysis are reported here. The lens was removed with ease in patients 30 years of age and over, who were exposed to the active enzyme effect for

three minutes in a concentration of 1:5,000 or (150 Armour proteolytic activity units per cc.). The aqueous chamber was irrigated in all cases. The material used was Alpha Chymar® in 75 cases and the Spanish product Quimotrase® in two cases.

Alpha chymotrypsin facilitated intracapsular cataract extraction. It thus helped to prevent the complications of capsule rupture and of undue zonular traction on structures of the inner eye.

Special care is required to prevent contamination of the diluted enzyme by chemicals which might cause inhibition or inactivation of alpha chymotrypsin.

Alpha chymotrypsin did not produce zonulolysis in an 18-year-old young man with traumatic cataract. The three-minute period of enzyme action was probably too short for a patient of this age.

With use of alpha chymotrypsin, there is a tendency to lift the lens during cataract extraction without counterpressure. This can lead to complications. Failure to tuck the cornea against the capsule of the advancing lens so as to help expression apparently was followed in one case by vitreous prolapse, in another by vitreous presentation. Both occurrences were evidently due to a strong attachment between the posterior lens capsule and the hyaloid (negative pressure or a strong resistant Wieger's ligament or both). The use of the squint hook or any similar instrument to hold the cornea against the lens so that Wieger's ligament and the hyaloid would be stripped from the capsule resulted in prevention of the tendency for vitreous to follow the loosened lens.

Mild striate keratitis appeared in 60 percent of 40 patients operated with alpha chymotrypsin and vacuum cup. It was an infrequent and negligible factor in the group of cases operated with capsule forceps. The slightly bulky vacuum cup was presumed to have mechanically damaged the corneal endothelium causing corneal edema.

Mild transient uveitis was found to occur more frequently in patients operated with the

Bell erisophake than in a similar group operated with capsule forceps. It was also considered to be secondary to the corneal insult.

The zonula showed a varying but mild change in texture after use of alpha chymotrypsin. It appeared somewhat grayish and thinner. Some of its landmarks had become undistinguishable. However, the zonular membrane was visible, though somewhat altered, in all of the 52 cases submitted to gonioscycloscopy. Evidence seems to point to the predilective lytic action of alpha chymotrypsin on the zonular attachment to the lens capsule. The margin of the aphakic "zonular foramen" appeared somewhat irregular and also showed a mild deterioration of texture. It is possible that on longer exposure to the enzyme action, the entire zonula might have been digested.

Gonioscopic examination of the endothelial side of the healing incision pointed to a slight delay in the complete cicatrization of the inner side of the wound: 28.8 percent of cases showed a slight posterior cleft at the end of two months. A previous study of 318 cases without enzyme showed a cleft to be present in 21 percent of cases. In both instances two thirds of this percentage showed further closure within another month. The series is too small to draw final conclusions.

Subluxation of the crystalline and presence of vitreous in the anterior chamber appears to be a contraindication to the use of alpha chymotrypsin.

Endothelial dystrophy may be a contraindication for use of alpha chymotrypsin. However, a case of endothelial dystrophy with early epithelial change in which enzyme was unintentionally used showed no aggravation of the process two months following surgery. It is too early to judge what the future course will be. One case is a hazardous source for the drawing of conclusions.

Ocular sensitivity to the enzyme was not observed.

Alpha chymotrypsin is a useful adjunct to cataract surgery. It need not be routinely used in older patients. It appears to be un-

necessary for most patients over 65 years of age.

An occasional old patient, particularly the one with a tough zonule, has a definite indication for the use of alpha chymotrypsin.

Alpha Chymotrypsin appears to be a valuable and safe addition to the technique of intracapsular cataract extraction.

Alpha chymotrypsin has taken the moment of anxiety or call it "thrill" out of cataract surgery. The use of alpha chymotrypsin for zonulolysis can serve to relieve that moment of anxiety for the cataract surgeon when he meets up with a tough zonula.

It will take a longer period and larger series for a full evaluation of enzymatic zonulolysis.

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ADDENDUM

Biomicroscopic examination of 42 lenses extracted in capsule shortly after their removal by me revealed them to be either en-

tirely devoid of zonular fibers (bald) or to show a count of one to 15 remnants of zonular fibers. Sometimes these appeared bunched and tangled at the equator. Two showed an apron or frill of narrow membranous anterior zonular leaf attached just anterior to the lens equator.

Goniocycloscopy of aphakic eyes operated by enzymatic zonulolysis with alpha chymotrypsin and biomicroscopy of cataractous lenses promptly after extraction, lead me to the following conclusions:

1. The anterior and posterior zonular membranes separate from the lens capsule at their attachment sites thereto. (This creates a new orifice, the "zonular foramen.")
2. A lysis of individual groups of zonular fibers occurs near their attachment to the lens capsule or at some midpoint between the lens and their posterior origins.
3. In rarer instances fragments of the anterior zonular leaf may come away with the extracted lens.

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FUNCTIONAL RESULTS WITH CONTACT LENSES IN UNILATERAL CONGENITAL CATARACTS, HIGH MYOPIA AND TRAUMATIC CATARACTS*

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There are few ophthalmologic problems whose solution is more rewarding than those in which a relatively useless eye is made useful. Amblyopia ex anopsia is not seen often in one-eyed individuals but, when it is, ophthalmologists wonder why someone could not have made a useful eye for that patient earlier in life. More important and occasionally more dramatic is the functional result produced in those cases of amblyopia which have been neglected, ignored, or partially treated because of the associated problem of anisometropia. The anisometropia is the basic difficulty in the group of patients to be reported. The discussion and outline presented is not considered ideal but is a method of treatment which in our hands and from the reports of others¹⁻⁹—as applied to

adults—and to children¹⁰ has given satisfactory results. There are many points of argument—physiologic, economic, anatomic, surgical, psychologic, and optical. Some of these will be mentioned in passing but the prime consideration is the percentage of functional results.

The main groups to be discussed are:

1. The young congenital unocular cataract patient made aphakic by successful surgery.
2. The patient with congenital high anisometropia, either myopic or hyperopic.
3. The patient with traumatic cataract made aphakic by successful surgery.

Anisometropia means a difference in the refraction of the two eyes. In small amounts of anisometropia there may be no difficulty. This is because the retinal images formed are of approximately the same size. Further, it is obvious that anisometropia does not nec-

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essarily mean aniseikonia. This depends upon whether the anisometropia is corneal, lenticular, or axial. In high degrees of anisometropia, however, aniseikonia is generally present. Aniseikonia means a difference in the size of the retinal images. Actually there should be such a term as physiologic aniseikonia. This would infer a difference in retinal image size, as interpreted by the brain, which would cause a disparity in the actual form of the image presented, or produce asthenopia. This is the basis of the work done by Ames¹⁵ in which normal persons could tell a difference in image size of 0.85 percent and the average size difference in clinical cases was 1.54 percent.

Cowan¹¹ states that each 0.25D. difference in the refraction causes about 0.5-percent difference in size between the two retinal images. He further states that there are many instances in which a limit greater than five percent is tolerated without any discomfort whatever. This would certainly follow the average findings in routine refractions in which one infrequently has problems in less than two diopters of difference in the refraction.

There is, however, a more important consideration. The capacity for fusion is proved by combining two different pictures, for example, the bird in the cage. This is first-degree fusion.

Second-degree fusion is the ability to perceive the images of some objects which have both similar and dissimilar components and combine or fuse them, and hold them against a certain amount of disjunctive movement, for example, a similar girl with different balloons fused and held against convergence and divergence.

Third-degree fusion is the ability to combine two slightly dissimilar unocular presentations into a unitary perception with the correct conception of space; that is depth perception or stereopsis. The word slightly describes the problem. There is no doubt that the smallest amount is the minimal variance perceptible. That which is the largest pre-

sents the major problem. To have third-degree fusion, the images must not fall on exactly corresponding retinal points but rather must touch slightly separate retinal points. Thus the image size must vary to be fused. This would represent another type of physiologic aniseikonia, or that which is normally interpreted by the brain. I am unable to state what this limit is but must fall back on empirical findings, mine and others. A figure of less than 10 percent would seem reasonable. Further, there must be a difference in foveal, macular, and perimacular limitations. A possible maximum could be calculated by noting that there is a 28-percent difference in the weather vanes on one of the Keystone stereoscopic cards, and yet they are easily fused.

Using the formula $\frac{\text{object}}{\text{image}} = \frac{f}{f'}$, as in the

diagram (fig. 1), where the object (the weather vane) would be two cm. held at 10 cm. from the eyes or f (the distance from the object to the anterior principal focus), and f' is the anterior principal focal distance (1.7) the image size comes out to be 3.4 mm. This must thus mean a certain amount of perimacular fusion as the limits of the macula is usually given as one to three mm. Further, in regard to third-degree fusion and image size it is generally felt that peripheral fusion is a strong factor. Scobee¹⁰ emphasized this and further felt that one might have perimacular and macular fusion simultaneously without foveal fusion. This may account for the lack of asthenopia, diplopia, or suppression in not only the routine lower degrees of anisometropia but in the small but definite amounts of aniseikonia ultimately produced in the groups being discussed.

The fusional development of the child normally starts at a relatively early age. Binocular ability, that is, as Gesell¹² indicates, the ability of the child to perform for the examiner, can be elicited as early as the third year, and progresses to completion by about the eighth year. At the age of two years most

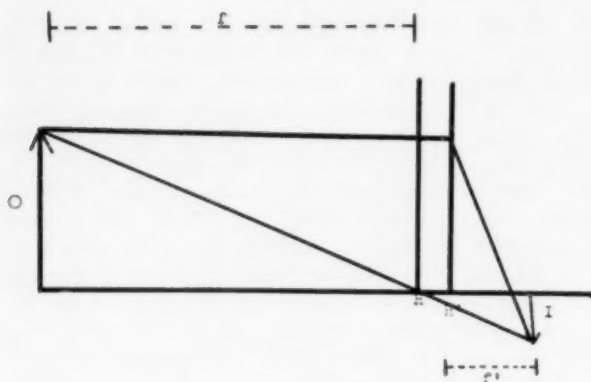


Fig. 1 (Spaeth and O'Neill). Diagrammatic representation of the factors determining the size of an optical image. The size of the image (I) is in the same ratio to the size of the object (O) as the distance (f') is to the distance (f). An increase in (f') must result in an increase in the size of (I).

children show evidence of binocularity which is, in itself, an indication of a learning process or function which has taken time to develop. It is well known that amblyopia can be broken down far more effectively at the age of three years than at the age of eight years, and after about the 10th year, the majority of cases are quite hopeless. It is obviously futile to try for binocular vision unless there is no amblyopia or only a relative amblyopia. In my experience, 6/15 (Snellen chart) is satisfactory vision in the poorer eye to warrant the attempt to induce binocular vision. In any event, therapy must be started early.

THE FIRST GROUP

This group with unocular congenital cataract may also include binocular congenital cataracts in which one cataract is more obstructive than the other.

Some years ago Duke-Elder¹³ recommended early surgery. My preference, in general, is during the third year. The aphakic correction must be found and ordered as soon as possible following completion of the surgery. The normal eye is constantly occluded until the best visual acuity of the aphakic eye is obtained. This will not infrequently take two or three months. This process, not the surgery, is frequently the most difficult. It may be necessary to refract the child several times, even doing a refraction under general anesthesia. The child will not learn to see if the correction is faulty.

Occasionally, commencement of occlusion is very difficult. In rare instances it may be necessary to use a light plaster of paris head cast to start occlusion. A co-operative mother is a necessity. Transference amblyopias have occurred, though these are relatively no problem. If there is an associated strabismus, this must be corrected. When the child's visual acuity is 6/15 or better, it is time for the final optical correction—the contact lens.

THE SECOND GROUP

The congenital high anisometropia is best illustrated by the child with one highly myopic eye and one emmetropic eye. This child will occasionally learn to alternate, using the myopic eye at near and the emmetropic eye at distance. Usually, however, an amblyopia develops in the ametropic eye, and frequently there is an associated strabismus. It is interesting to contemplate that these children have suppression or strabismus because of an optical block to fusion rather than a neurophysiologic lack of fusional ability.

These children are treated as follows: an accurate refraction, the refraction ordered, constant occlusion of the good eye until 6/15 or better vision is obtained, and the strabismus corrected; then the child is ready for the contact lens.

THE THIRD GROUP

The traumatic cataract is most frequently seen. These cases usually have the advantage

of having had good vision prior to the formation of the cataract and binocularity is already a learned function. Early treatment in this group is the most rewarding. Procrastination will allow strabismus to develop and, in the youngest patients, relative amblyopia will develop. Early cataract surgery may eliminate the need for strabismus surgery or for occlusion, and the child will then be ready for the contact lens as soon as the operative reaction subsides and refraction can be done.

It must be emphasized that the nonsurgical steps are hardest and take the most time. The parent can be easily antagonized over the child's unhappiness with occlusion. Every effort must be made to explain the various procedures or else one may lose more than the usual number of patients. The greatest failure comes from the lack of constant occlusion.

The correction of an anisometropia by regular glasses produces, of course, a difference in image size. This is spectacle magnification, as termed by Bennett.¹⁴ It may be defined as the ratio of the retinal image size in the corrected ametropic eye to that in the uncorrected eye, having reference to an object at infinity. Spectacle magnification is always greater than unity for a convex lens and less than unity for a concave lens. Using Bennett's figures we may compare a myopia of -20D. with regular glasses and with a contact lens. In a myopia of -20D. (spectacle refraction at 12 mm. from the cornea), the spectacle magnification is 0.77 for orthodox glasses and 0.955 for contact lenses. The percentage increase afforded by contact lenses is therefore:

$$\frac{0.955 - 0.77}{0.77} \times 100 = 24 \text{ percent.}$$

Thus an image size 24-percent larger would be formed by the contact lens in the myope and, consequently, there would be that much less aniseikonia and thus that much more chance of fusion.

Now consider the artificial hypertrope, the aphakic patient. Just as the contact lens

magnifies the image in myopia relative to glasses, so does the contact lens minify the image in aphakia as compared to glasses. We shall use Gullstrand's schematic eye as the basis for the calculation. Removal of the crystalline lens reduces the power from 59.60D. to 43.08D. For correction here an 11.2D. lens is needed 12 mm. from the cornea. This would have an equivalent power of 48.45D., or a retinal image size increase of:

$$\frac{59.60}{48.45} = 1.23 \text{ or 23-percent increase.}$$

Thus, presumably, we have an image 23-percent greater than the normal eye.

If a contact lens were now used with a minifying effect which is calculated¹⁴ as 0.88 the percentage increase would be:

$$0.88 \times 1.23 = 1.08$$

or only eight-percent greater than the normal aphakic eye.

Rockwell's⁴ calculations produced an image size in the aphakic eye, with a contact lens of 5.34-percent larger than that of the aphakic eye. This assumed the lens contributed nothing to the thickness of the cornea. However, even with the thickness of the contact lens as one mm., a generous maximum, his maximum size difference was only 9.85 percent.

The patients of Constantine and McLean⁹ whom Linksz measured on the eikonometer were found to have an image size difference of only seven to eight percent. All these figures are in relative concurrence and make it obvious that the contact lens produces much less aniseikonia.

Another point to mention is the prismatic imbalance which exists in the correction of ametropia with a spectacle lens, when ametropia, antimetropia or high astigmatism exist. This is due to the fact that a spectacle lens acts as a prism at all points away from its optical center. With a +10D. lens in front of the right eye and the eyes turned to the left, the prism effect would be base-out and the light ray bent to the temporal side of the retina, as in Figure 2. This produces

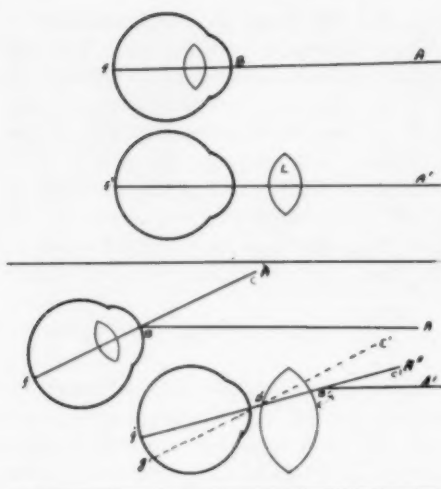


Fig. 2 (Spaeth and O'Neill). Diagram demonstrating prism effect.

an artificial exophoria which would have to be overcome by convergence. There would be an artificial esophoria if the eyes were turned to the right. Exactly the reverse would occur in myopia. Even worse is the fact that it is a noncomitant problem. It may be that this is of even greater importance than size difference in the ability of the patient to acquire fusion. The contact lens negates this problem.

TYPE OF CONTACT LENS

In children the scleral rest type contact lens gives the best results. The corneal lens slides off the cornea much too easily in an active child. It is actually more difficult for the parent to use and far too difficult for the child to use when he becomes old enough to take care of it himself (at about 10 years of age). Any operative scars make adjustment of the corneal lens almost impossible. We have found the vented scleral lens the most satisfactory. Of course, in the aphakic patient a +3.0D. must be used in some form of reading lens or bifocal.

In the last several years we have had about 50 children with basic high anisometropic problems. Twelve of them have

been starting failures in that their visual acuity could not be brought up to 6/22. This was either due to a failure of surgery or occlusion. Ten are still in the preliminary stages of treatment or have not yet received their contact lenses. Several patients drifted away either immediately or shortly after the program was started. Twenty-four of the patients have achieved a visual acuity of 6/15 or better. Four of them who needed strabismus surgery were fitted with contact lenses. Table 1 summarizes the wearing time, fusion, age, visual acuity, and number of years worn.

PERCENTAGE OF PATIENTS WITH THIRD-DEGREE FUSION

Most remarkable is that 71 percent of the patients achieved third-degree fusion. This is fusion tested on stereoscopic cards and amblyscopes, and the Wirt stereotest. With the latter, most patients achieve a Shepard rating of 70 percent. Moreover, the cosmetic improvement is excellent; these children look well as they are fusing.

CASE REPORTS

CASE 1

J. G., aged seven years, was seen because of poor vision in the right eye. The child's visual acuity was 6/150 in the right and she was unable to use the pinhole. Her visual acuity was 6/6 on the left. Atropine refraction revealed on the right a -6.0D. sph. \ominus -2.25D. cyl. ax. 165°, with visual acuity corrected to 6/60 and on the left by a +0.5D. sph. \ominus +0.5D. cyl. ax. 85°, with uncorrected visual acuity of 6/6. The patient had an esotropia of 18 diopters with a slight left hypertropia. The refractive correction was ordered and occlusion of the left eye was started. At the end of three weeks corrected vision in the right eye was 6/22. At the end of two months, the visual acuity of the right eye had increased to 6/9. At this time a contact lens was ordered for the right eye and no correction for the left eye. With a contact lens on the right eye, the child was found to have first-degree fusion with slight second-degree fusion. The tropia was thus actually a phoria.

CASE 2

E. D., aged six years, was first seen with a diagnosis of congenital cataract on the left eye. His visual acuity was 6/6 in the right and 2/60 in the left eye. He had an uneventful linear extraction with peripheral iridectomy, left eye, followed by a capsulotomy 10 days later. His visual acuity, with

TABLE 1
SUMMARY OF CASES

Condition	Patient	Wearing Time (hr.)	Fusion	Age (yr.)	Visual Acuity	Years Worn
Cases made aphakic by trauma	D. J.	12	0	7	6/22	1
	R. C.	8	3	9	6/5	1
	W. A.	12	3	10	6/5	4
	R. P.	13	3	16	6/7.5	4
	D. H.	11	3	12	6/5	2
	R. W.	10	3	10	6/5	5
	R. W.	9	3	14	6/6	4
	G. R.	9	3	12	6/9	2
	P. B.	7	1	15	6/12	7
	L. H.	10	1	17	6/12	4
	J. W.	10	3	12	6/7.5	4
	D. S.	poor	0	9	6/15	0
	R. B.	10	3	12	6/6	2
	R. G.	14	1	8	6/6	2
Congenital cataract	J. S.	12	3	16	6/6	3
	E. D.	9	3	8	6/6	3
	K. O.	8	0	5	6/7.5	2
Myopia	J. G.	10	3	8	6/7.5	2
	C. S.	13	3	12	6/6	3
	L. L.	13	3	9	6/12	3
	R. P.	8	3	10	6/7.5	2
	C. B.	8	2	8	6/9	1
	R. G.	14	3	14	6/7.5	1
Hyperopia	W. P.	12	3	7	6/12	1
Average age of children when first seen		8 yr.				
Average wearing time (contact)		9+ hr.				
Average fusion		2°+				
Average age of children now		12 yr.				
Average number of years contact worn		3+ yr.				
Average visual acuity		6/7.5				

a +10D. sph. and pinhole, following convalescence, was 6/45. Atropine refraction revealed an emmetropic right eye and a refractive error of +15D. sph., left eye. Because there was no evidence of deviation and because the child was over six years of age, he was sent for his contact lens immediately and a +3.0D. sph. bifocal for the left eye. Following several months of occlusion and repeated grindings to the contact lens, his visual acuity increased to 6/12. At that time the child was placed on intermittent occlusion and orthoptic exercises, as he was developing a convergence insufficiency. One and one-half years following the original surgery, visual acuity had improved to 6/6. The child had first-, second-, and third-degree fusion with a near-point of nine cm.

CASE 3

R. B., age 10 years, had never worn glasses. A traumatic cataract in the left eye resulted from a direct blow with a stone. The visual acuity was 6/6 on the right and 1/60 on the left, with good light perception and projection. The slitlamp revealed a dense, slightly swollen cataract. The patient had an uneventful linear extraction on the left with the resulting visual acuity, with a +10D.

sph. pinhole, of 6/12. His first postoperative refraction was: O.D., +6.75D. sph. (atropine cycloplegic); O.S., +14.5D. sph. (aphakic). The patient was sent for his contact lens and this prescription: R.E., +4.0D. sph.; L.E., plano with a +3.0D. sph. bifocal. Unfortunately, it was three months before the child obtained his contact lens; and in this time he developed an esotropia of 15 diopters at far and 25 diopters at near. The visual acuity over the next three months decreased to 6/22 because of capsular changes in the left eye; consequently, the child had a capsulotomy seven months following his original surgery. This brought the child's visual acuity with his contact lens to 6/6 in the aphakic eye. His esotropia increased to 25 diopters at near and 11 months following the original trauma, the child had a recession of the medial rectus muscle on the left and a resection of the lateral rectus muscle on the left. Following the cessation of the operative reaction the child had first-, second-, and third-degree fusion with his contact lens.

SUMMARY AND CONCLUSION

The basic problem of high anisometropia should not deny a child the advantages of

fusion in a large percentage of cases. To overcome the problem takes a lot of effort, but the functional and, therefore, cosmetic results are good. It is necessary to institute early treatment if the desired result of first-,

second-, or third-degree fusion is to be obtained. The use of corrective contact lenses gives most satisfactory results.

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USE OF BC-48 (DEMECARIUM BROMIDE) IN TREATMENT OF GLAUCOMA*

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INTRODUCTION

Anticholinesterase agents are of value in the treatment of glaucoma. Several cholinesterase inhibitors have been tried in its

management from time to time. Among the short acting cholinesterase inactivators physostigmine (eserine, introduced by Laqueur) and neostigmine (prostigmine, introduced by Rossi) are the drugs of choice. Of the long-acting cholinesterase inactivators DFP (Floropryl, introduced by Leopold and Comroe), TEEP (tetraethylpyrophosphate, introduced by Grant), Bayer E600 (Mintacol, introduced by Thiel, and Gles and Wustenburg) have so far been the most popular agents, and 217-MI (echothiophate, phospholine iodide, introduced by Leopold, Gold and Gold) promises to be a very useful agent. BC-48 (demecarium bromide, introduced by Gittler and Pillat) a new long-

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acting cholinesterase inhibitor forms the subject of the present study.

BC-48 (generic name: demecarium bromide; chemical name: decamethylene bis [N-methylcarbaminoyl - m - trimethylammoniumphenol bromide]) is the most powerful of the synthetic cholinesterase inhibitors belonging to the group polymethylene-bis-(N-methylcarbaminoyl - m - trimethylammoniumphenols, Kraupp, Stumpf, Herzfeld and Pillat; Kraupp, Schwarzacher and Stumpf). It combines with true or specific cholinesterase mainly and readily (Herzfeld and Stumpf; Leopold, Krishna and Lehman). In addition it possesses certain inherent muscarinic properties by virtue of being a quaternary ammonium compound (Pillat, Stumpf, Gittler and Pommer). It is soluble in water and is stable for indefinite periods under ordinary conditions (Gittler and Pillat).

Gittler and Pillat, and Krishna and Leopold have shown that in normal rabbits and human eyes BC-48 produces rapid, marked and prolonged miosis accompanied by congestion of the eye, spasm of accommodation and ciliary pain. Miosis of BC-48 is easily abolished by atropine and homatropine. Miosis is easily induced by BC-48 in atropinized and homatropinized eyes. BC-48 produces lowering of intraocular pressure and increase in the coefficient of aqueous outflow facility after one local application to normal eyes which last for several days (occasionally some eyes show a rise in intraocular pressure). No permanent damage has been detected in the eyes treated to date. BC-48 induces some systemic muscarinic and nicotinic effects in some normal human subjects and rabbits, when instilled locally into the eyes. Physostigmine when given first does not block the action of BC-48 in normal rabbits.

Gittler and Pillat's study on the use of BC-48 in the treatment of glaucoma was confined to its use for a period of less than two weeks in the majority of cases. In their study only one strength of BC-48,

that is, one-percent aqueous solution was employed. Miller, Divert and Crouzet utilized only 0.5-percent concentration of BC-48. Gougnard studied the tension-lowering effect of BC-48 after a 24-hour period in a very small series of glaucoma cases when employed in the strength of 0.1 to 0.5-percent solution. Consequently the present investigation was undertaken to determine the efficacy of BC-48 when observed in a larger series, for a longer period of time and employing various concentrations.

METHODS

Materials. A total of 106 glaucomatous eyes of 59 patients were tested with BC-48 during a period of six months. These cases were picked at random, regardless of the type of glaucoma, from the clinics of Wills Eye Hospital. Included in this series are also six eyes of three cases with angle-closure glaucoma (acute and subacute) from private practice. All of them were treated with the usual antiglaucoma agents prior to the use of BC-48.

Aqueous solution of the compound BC-48 was employed. The solution was kept at ordinary room temperature. The concentrations employed were 0.1, 0.25, and 0.5 percent and the frequency of instillation varied from twice a week to twice daily. An attempt was made to use the weakest concentration of BC-48 which when used alone as infrequently as possible would control the intraocular pressure. In some eyes with chronic wide-angle glaucoma acetazolamide (Diamox) 125 mg. to 250 mg. two to four times a day orally was used in addition, if BC-48 alone failed to control intraocular pressure. The clinic visits varied from twice a week to every two weeks. A small percentage of cases were hospitalized and later on followed in the outpatient clinic. On each clinic visit ocular tensions were measured with Schiøtz tonometer and visual acuities recorded with Snellen's charts. Visual fields both peripheral and central were checked at regular intervals with perimeter and one-meter tangent

screen respectively. Gonioscopic examinations were done at periodic intervals using the Koeppe lens, Barkan hand illuminator and the Goldmann biomicroscopic head. Repeated tonographic tracings were obtained, using the Mueller electronic tonometer connected to a Leeds and Northrup recorder. Ophthalmoscopic and biomicroscopic examinations were done at repeated intervals.

Based on these examinations, a case was considered to be controlled, which for a minimum period of four months showed: consistently lower tensions which never exceeded 25 mm. Hg (Schiotz); no loss of visual acuities which could be explained on the basis of glaucoma; no further loss of visual fields; no new peripheral anterior synechias or goniosynechia formation; increase in the coefficient of aqueous outflow facility above 0.16 cu. mm./min./mm. Hg or a definite increase as compared to the original value; no further increase in glaucomatous cupping; no complications such as retinal detachment, iris cysts, synechias, atrophy and corneal epithelial bullae or corneal edema. Cases which did not fulfill these criteria or in which therapy had to be discontinued because of local or systemic side-effects were classified as uncontrolled. Patients who refused medication after one to three days merely because of the symptoms of ciliary spasm were not included.

TABLE 1
TYPES OF GLAUCOMA TREATED WITH BC-48
(DEMECARIUM BROMIDE)

Type of Glaucoma	Number of Eyes	
1. Open-angle	80	
a. Noncongestive	75	
b. Congestive	5	
c. (Absolute)*	(6)	
2. Angle-closure	20	
a. Acute	6	
b. Subacute	14	
c. (Absolute)†	(1)	
3. Secondary	6	
a. Aphakia	4	
b. Uveitis	2	
TOTAL	106	

* Included in the noncongestive group of open-angle type.

† Included in the subacute group of angle-closure type.

RESULTS

Table 1 summarizes the types of glaucoma treated with BC-48. Of the total of 106 eyes, 80 eyes had open-angle type, 20 angle-closure type, and six secondary type of glaucoma.

Table 2 summarizes the results on these 106 eyes. Favorable results were obtained when BC-48 therapy was employed (87 controlled and 19 uncontrolled) compared with previous therapy (49 controlled and 57 uncontrolled) in all types of glaucoma.

Table 3 shows the duration in months for

TABLE 2
SUMMARY OF RESULTS ON 106 EYES

Type of Glaucoma	Controlled on Previous Therapy (No. of eyes)		Uncontrolled on Previous Therapy (No. of eyes)		Controlled on BC-48 Therapy (No. of eyes)		Uncontrolled on BC-48 Therapy (No. of eyes)	
<i>Open-angle</i>	42		38		65		15	
Noncongestive	41		34		60		15	
Congestive	1		4		5		0	
(Absolute)	(2)		(4)		(4)		(2)	
<i>Angle-closure</i>	4		16		17		3	
Acute	0		6		3		3	
Subacute	4		10		14		0	
(Absolute)	(0)		(1)		(1)		(0)	
<i>Secondary</i>	3		3		5		1	
Aphakia	2		2		3		1	
Uveitis	1		1		2		0	
TOTAL	49		57		87		19	

TABLE 3
DURATION OF BC-48 (DEMECARIUM
BROMIDE) THERAPY

Number of Months	Number of Eyes Controlled
4	34
4-5	17
5-6	9
6-7	14
7-8	13
TOTAL	87

which 87 eyes were controlled successfully on BC-48 therapy.

Table 4 compares the dosage of BC-48 therapy and previous therapy in the same controlled eyes which total 49. In all except two eyes the glaucoma was controlled on BC-48 alone. These two eyes needed acetazolamide (Diamox) in addition to bring them under control. The use of BC-48 alone, its lower concentrations and the relative infrequency of instillation are in marked contrast to the combined use of various antiglaucoma agents, their greater concentrations and the more frequent instillations required to bring about the control of glaucoma in the same eyes.

Table 5 records the effect of BC-48 therapy on the facility of aqueous outflow of some of these glaucomatous eyes. In most of the eyes where intraocular pressure was brought under control there was an increase in the coefficient of aqueous outflow facility.

In some there was an actual embarrassment in the outflow facility within the first few hours. In two eyes which were controlled on previous therapy and not on BC-48 therapy, there was an actual decrease in the coefficient of aqueous outflow with the coincident increase in intraocular pressure.

There were 19 eyes uncontrolled on BC-48. These included two eyes in which there was an actual increase in intraocular pressure with BC-48 which were otherwise controlled on previous therapy. One eye of a patient with bilateral chronic narrow-angle glaucoma, developed corneal edema during the course of BC-48 therapy though the pressure had not risen; the edema cleared on cessation of BC-48 therapy and after a basal iridectomy. The other eye of the same patient was well controlled on BC-48 therapy without any local side-effects. One glaucoma subject developed nausea, vomiting and diarrhea after one single instillation in each eye and the BC-48 therapy was discontinued; there were two eyes of another glaucoma patient in whom BC-48 had to be discontinued because of difficulty in breathing, feeling of constriction of chest and sinking sensation in the precordium after one single instillation. This patient gave a history of bronchial asthma.

The majority of patients complained of browache, headache, pain localized in the globe and transient blurring of vision, which

TABLE 4
COMPARISON OF DOSAGE OF BC-48 (DEMECARIUM BROMIDE) THERAPY AND OTHER
GLAUCOMA THERAPY IN THE SAME CONTROLLED EYES

No. of Eyes	Previous Therapy	BC-48 Therapy
12	Pilocarpine 1% tid-qid	0.1% twice a week, once daily
13	Pilocarpine 2% tid-qid	0.1%-0.25% twice a week-bid
3	Carcholine 1.5% tid-qid	0.1% twice a week, once daily
2	DFP 0.05-0.1% od-bid	0.1% twice a week, alternate days
3	217-MI 0.1-0.25% od-bid	0.1% twice a week, alternate days
3	(Pilocarpine 3% tid-qid + Physostigmine 0.5% tid-qid + Diamox 125 mg.-250 mg. bid-qid)	0.25%, once daily, bid
13	(Pilocarpine 4% tid-qid + Physostigmine 0.5% tid-qid + Diamox 125 mg.-250 mg. bid-qid)	0.25-0.5%, once daily, bid*
49 (TOTAL)		

* Diamox (125 mg.) bid in addition to 0.25% BC-48 bid in two eyes.

TABLE 5
EFFECT OF BC-48 (DEMECARIUM BROMIDE) THERAPY ON THE FACILITY OF
AQUEOUS OUTFLOW OF GLAUCOMATOUS EYES

Patient	Time	Coefficient of aqueous outflow facility in mm./min./mm.Hg	
		O.D.	O.S.
1. M.C.	No medication for 60 hr.	0.13	0.10
	2 hr. after continuation of BC-48 therapy	0.17	0.17
2. W.B.	No medication for 48 hr.	0.13	0.14
	2 hr. after continuation of BC-48 therapy	0.15	0.15
3. J.M.	No medication for 6 hr.	0.13	0.09
	6 hr. after continuation of BC-48 therapy	0.13	0.11
4. E.M.	No medication for 36 hr.	0.07	0.09
	24 hr. after continuation of BC-48 therapy	0.10	0.17
5. A.C.	No medication for 24 hr.	0.27	0.13
	23 hr. after continuation of BC-48 therapy	0.26	0.16
6. N.T.	No medication for 36 hr.	0.05	0.07
	68 hr. after continuation of BC-48 therapy	0.04	0.14
7. A.F.	No medication for 48 hr.	0.07	0.09
	68 hr. after continuation of BC-48 therapy	0.11	0.10
8. D.I.	No medication for 24 hr.	0.10	0.08
	24 hr. after continuation of BC-48 therapy	0.19	0.19
9. D.N.	No medication for 8 hr.	0.07	0.03
	24 hr. after continuation of BC-48 therapy	0.10	0.05
10. H.D.	No medication for 24 hr.	0.05	0.08
	3 hr. after continuation of BC-48 therapy	0.07	0.08
11. L.T.	No medication for 48 hr.	0.04	0.06
	2 hr. after continuation of BC-48 therapy	0.08	0.07
12. I.T.	No medication for 48 hr.	0.13	0.09
	3 hr. after continuation of BC-48 therapy	0.06	0.09

lasted for two to three days after instituting BC-48 therapy. Conjunctival injection both superficial and deep persisted for a few days initially and then gradually subsided. The incidence of these symptoms was higher in patients who had formerly employed pilocarpine alone in contrast to those who had been using an anticholinesterase agent in addition. All these symptoms disappeared a few days after continued BC-48 administration. There has been no incidence of iris cysts, retinal detachment, local sensitivity reaction, follicular conjunctivitis or iritis in the present series.

CONCLUSIONS

The present study confirms the findings of Gittler and Pillat, Gougard, and Miller,

Divert and Crouzet that BC-48 is an effective agent in the control of glaucoma. It appears to control intraocular pressure even in eyes uncontrolled on conventional glaucoma therapy.

Regarding its evaluation as an ideal anticholinesterase agent in ophthalmology according to the criteria laid down by Krishna and Leopold in the evaluation of echothiophate (phospholine iodide) (217-MI) it possesses the following distinct advantages:

1. BC-48 is a potent, long-acting cholinesterase inhibitor with great intensity and duration of action. Concentrations of 0.1, 0.25 and 0.5 percent, used as little as twice weekly to twice a day, control intraocular pressure in eyes with various stages and types of glaucoma. It offers the distinct advantage

of infrequent instillations and reduction of the diurnal fluctuations. It eliminates the undesirable need of administration of therapy during the sleeping hours.

2. BC-48 is readily soluble in aqueous solution. It is indefinitely stable under ordinary conditions and does not deteriorate at room temperature. Thus it offers the advantage of easy storage and freedom from sensitivity reaction due to the vehicle employed in dispensing some anticholinesterase inhibitors.

3. BC-48 seems to be synergistic with other anticholinesterase agents and unlike DFP or 217-MI, its action is not blocked when eserine is given first. Thus it has the advantage that good results may be expected even when other anticholinesterase agents have been used previously in the same eye.*

BC-48 however possesses certain disadvantages.

1. Locally it produces undesirable symptoms of spasm of accommodation, ciliary pain and vasodilation in most instances, which gradually disappear.

In some eyes it may cause paradoxical rise of tension.

2. Systemically it produces certain undesirable muscarinic and nicotinic actions.

Thus BC-48 is by no means an ideal anticholinesterase agent. But by virtue of certain advantages that it offers, it appears to be a useful cholinesterase inhibitor in the control of glaucoma.

Based on the present study the following conclusions may be made:

1. As low concentrations as will effectively control the intraocular pressure should be utilized. This should tend to reduce systemic toxicity.

2. Frequency of instillations should be de-

termined according to the individual cases. In no case should it exceed more than twice a day.

3. It may be combined with other anticholinesterase inhibitors where BC-48 alone or the other anticholinesterase agents fail to bring down the tension.

4. It should be used with caution in angle-closure glaucoma.

5. It should be used with caution where parasympathomimetic agents are contraindicated, namely marked vagotonia, vasomotor instability, bronchial asthma, spastic gastrointestinal disturbances, hypotension, myocardial infarction, epilepsy, Parkinsonism.

SUMMARY

BC-48 (demecarium bromide) a very potent long-acting anticholinesterase agent is described. Its use in the control of glaucoma using 0.1, 0.25 and 0.5-percent in aqueous solutions, twice weekly to twice a day in 106 glaucomatous eyes is discussed. Favorable results in 87 eyes with various types of glaucoma with BC-48 therapy are reported. The advantages and disadvantages of this new anticholinesterase inhibitor are discussed.

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* This observation is based on our experimental data on rabbit eyes and has been confirmed in two cases of acute glaucoma where tension could be brought under control only after the addition of BC-48, a course of mechoylol and prostigmine followed by pilocarpine and physostigmine along with Diamox having been tried before without any beneficial results. These observations are at variance with those of Gittler and Pillat and need further evaluation.

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THE PATHOGENESIS AND PATHOLOGY OF OCULAR ONCHOCERCIASIS

PART IV. THE PATHOLOGY

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The pathology of every ocular manifestation attributed to onchocerciasis is given here and this section contains microscopic proof of my claim that the posterior segmental lesions are of two types.

The following are the conditions described:

1. "Bung" eye
2. Limbitis
3. Superficial punctate keratitis
4. Sclerosing keratitis
5. Anterior uveitis
6. Posterior uveitis
7. Chorioretinal degeneration (the poste-

rior degenerative lesion of onchocerciasis)

8. Optic atrophy

1. "BUNG" EYE

This colorful descriptive term was coined by Owen and Hennessey¹² to describe a (permanent) swelling of the upper lids commonly found in association with ocular onchocerciasis. The usual explanation of the phenomenon has been that edema is the cause.

Macroscopically there is edema of the dermis in which many engorged vessels are present. The subcutaneous tissue, however,



Fig. 34. (Rodger). Patch type of punctate corneal opacity. Epithelial lesion (Hematoxylin-eosin, $\times 150$.)

showed in the four cases collected that deep to the dermis simple bilateral lobulated lipomas were present. It is interesting to note that a lipomatous change in onchocercomas is a common finding elsewhere in the body.

Microscopic appearance

The epithelium of the lid in the early stages of invasion is of the normal stratified squamous pigmented type. There is no evidence of invasion of the epidermis by capillaries. In the dermis, which is edematous, many foci of chronic inflammatory cells exist. A great number of microfilarial fragments may be found, some of them in the interstitial tissue of the underlying lipoma. Changes in the elastic are negligible. In long-standing cases, on the other hand, the epithelium has become atrophic and the subepithelial elastic lost. The blood vessels reveal swelling and proliferation of the endothelium and in many instances this has led to occlusion of the lumen. The internal elastic

laminae stain faintly, and there are signs of reduplication of vessels. The fibroblasts have proliferated somewhat, especially near the vessels. *O. volvulus* microfilariae were present in the lipomas in all our cases.

One concludes, although admittedly from somewhat slight evidence, that the toxic products of the dead microfilarial bodies probably act as a stimulant to the adipose tissue of the lid with the subsequent development of a lipoma. This bears a parallel to the increased activity of the fibroblasts in the stroma. The cause of the epithelial atrophy, the elastic degeneration (after the initial proliferation) and the vascular anomalies may also be toxic; more probably the toxic effect involves the blood vessels first, and most severely, so that the anoxia resulting

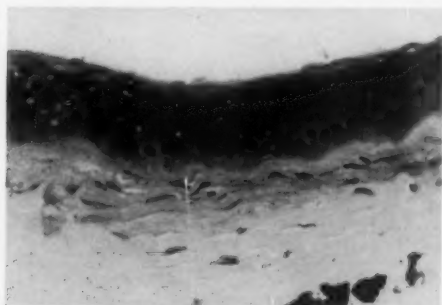


Fig. 35 (Rodger). Punctate corneal opacity in onchocerciasis subject. Subepithelial lesion. (Periodic acid-Schiff, $\times 150$.)

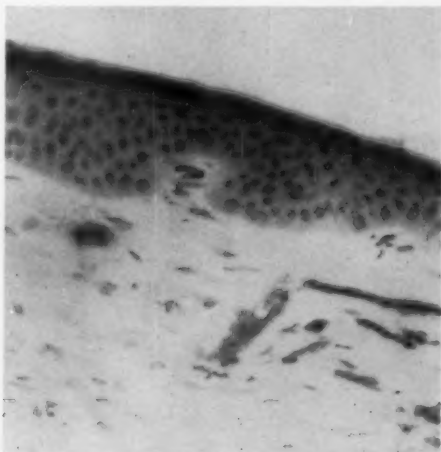


Fig. 36 (Rodger). Microfilaria of *O. volvulus* in epithelial cyst in cornea. Also subepithelial. (Hematoxylin-eosin, $\times 220$.)

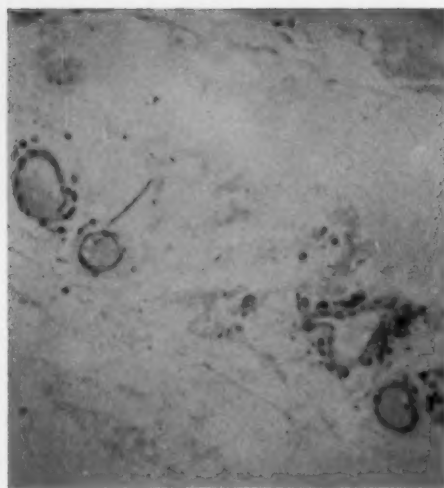


Fig. 37 (Rodger). *Microfilaria volvulus* in lipoma (Bung eye). (Hematoxylin-eosin, $\times 110$.)

from their subsequent occlusion is responsible for the epithelial and elastic atrophy.

2. LIMBITIS

There is hyperemia and chemosis of the bulbar conjunctiva and sclera at the limbus. The adjacent sector of the cornea frequently exhibits subepithelial opacification. Microfilariae are always present in biopsies of the overlying conjunctiva.

Microscopic appearance

There is a thick and pigmented conjunctival epithelium. Pigment is present in places in clear cells at all levels; this is to be expected in the negroid eye, of course, and is normal. There is no suggestion that the epithelium is keratinized, or even truly stratified, but there are one or two extra layers of polyhedral cells.

The underlying limbal lymphatics and vessels are characteristically somewhat dilated and new capillaries have sprouted here and there into the epithelium of the conjunctiva. In the subepithelial tissue there is a not inconsiderable infiltration of plasma cells along with a few eosinophil leukocytes and lymphocytes. Even in the early stages the

subepithelial elasticum seems to be affected and in contrast to the skin of the lid is soon lost from the area; in old cases the deep elastic as well as the vascular laminae are wholly destroyed.

Edema of the substantia is marked and there is evidence of increased fibroblastic activity, especially around the larger vessels. Where a limbitis was associated clinically with a "nodule" at the limbus, the latter always turned out to be a pinguecula. In some of the biopsies, a few capillaries were found projecting into the corneal tissue, usually but not always running between Bowman's membrane and the epithelium; they appeared in the crescent of corneal opacification. The latter was not due to edema and an overflow of inflammatory cells, as it seemed clinically, but to fibrosis; a few inflammatory cells were present, but too few to account for the clinical picture.

The biopsies were all taken from the 3- or 9-o'clock positions, close to the limbus, and included a small piece of the adjacent cornea. The question arises as to whether or not the changes found, especially in the case of the conjunctival epithelium, were due to the disease or to exposure, heat and malnutri-



Fig. 38 (Rodger). Bung eye. Simple lobulated lipoma. (Hematoxylin-eosin, $\times 110$.)

tion, all undoubted factors in the tropics.

A peripheral ring of corneal opacification running round the entire circumference of the limbus has been described elsewhere (Rodger¹³). At first sight it appears to be an arcus senilis. Microscopically it differs: it is never interrupted; it involves the anterior part of the stroma only; nor does it stain with Sudan III. It consists of fibroblasts and a few chronic inflammatory cells, which pass under the limbus without any lucid interval. I called this ring an arcus tropicalis, being convinced that it is caused by the climatic and dietary conditions prevailing in the tropics. However, in onchocercal limbitis, the corneal opacification corresponding to the arc of the limbus which is inflamed is superimposed in advance of any arcus tropicalis. Moreover, although it is difficult to conclude what the normal appearance of the epithelium may be in this part of the globe, it appears, in comparison with eyes not suffering from a limbitis, that there is in the latter a true metaplasia of the epithelium due to the parasites. About the remainder of the pathologic changes there can be no doubts: the vascular reaction is characteristic, as are the changes rung between proliferation and degeneration.

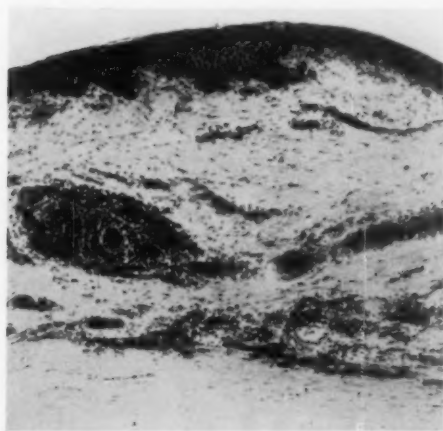


Fig. 39 (Rodger). Acute limbitis. One microfilaria volvulus (living) can be seen. (Hematoxylin-eosin, $\times 30$.)

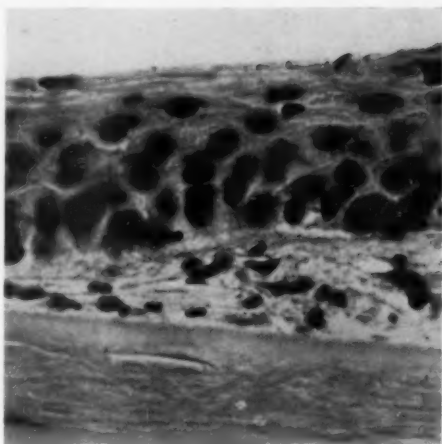


Fig. 40 (Rodger). Pannus onchocercosus. (Phloxine tartrazine, $\times 410$.)

3. SUPERFICIAL PUNCTATE KERATITIS

The opacities lie on either side of Bowman's membrane, and only occasionally more deeply in the stroma. I have used the descriptive terms *morula*, *patch*, and *halo* to describe the commonly present opacities as viewed with the slitlamp (Rodger¹⁴).

In the active stage of the keratitis, whatever its cause, it is the morula type which is found; this consists of a round collection of

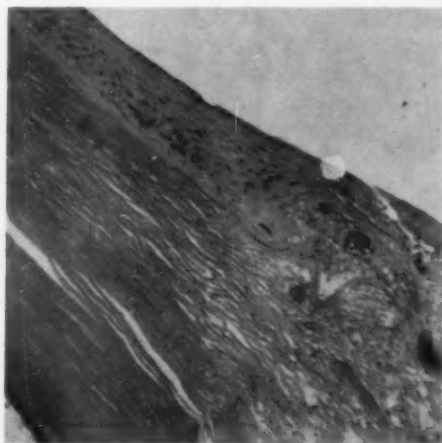


Fig. 41 (Rodger). Sclerosing keratitis, pigment in epithelium at base of pannus (zone 3). (Unstained, $\times 110$.)



Fig. 42 (Rodger). Chronic quiescent keratouveitis, with marked interstitial keratitis. (Masson, $\times 30$.)

discrete grayish-yellow dots like a mulberry. In onchocerciasis this collection is less likely to be round, being generally polyhedral and is usually much bigger in size than those due to a virus; punctate opacities can vary from 0.25 mm. to 2.0 mm., the larger being described as nummular by some workers; in most cases of onchocerciasis the greater diameter is the rule. The common appearance, then, is of a yellowish-gray opacity contiguous to the outer or inner side of Bowman's zone, usually polyhedral and about two mm. in diameter. As the disease continues the opacities are hidden by the greater involvement of the cornea consequent upon the development of a sclerosing keratitis. They may coalesce with each other or become part of the generalized keratitis, submerged in the advancing pannus.

In cases supposedly self-limiting, the punctuate keratitis frequently heals. As there is some doubt about the diagnosis and pathogenesis of the punctate lesions we cannot say for sure that all the opacities due to onchocerciasis heal; in those believed to be due to onchocerciasis, nevertheless, I have seen the individual dots of the morula fuse to form a uniform patch, which in turn started to clear from the center so that it

came to look like a halo, whence it continued to fade until no trace remained. Persistence of any shape or form on the other hand is common. Finally, it should be noted that this sequence of events is nonspecific, being equally relevant to any of the other types of punctate keratitis so commonly found in the tropics.

Microscopic appearance

Although I have excised many corneal opacities of the three descriptive types, the intention at the time was to ascertain whether or not microfilariae were present in them; the procedure adopted was to stain the excised opacity in bulk (it was surrounded by a margin of healthy cornea) and examine it on the flat. Parasites were never found. Where living microfilariae were seen with the slitlamp on several occasions the piece of cornea containing the parasite was excised, and subsequently blocked and sectioned; here no inflammatory reaction was ever observed. In two patients punctate opacities were excised, blocked and sectioned and stained variously; one of these cases suffered from onchocerciasis. As the opacity was of the patch type it enables us to give a

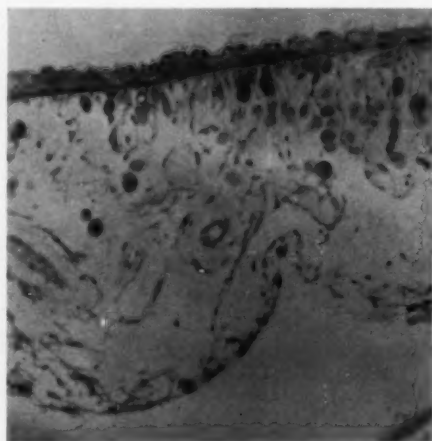


Fig. 43 (Rodger). Bleached negroid iris to show average distribution of clump cells in apparently healthy eye. (Phloxine tartrazine, $\times 110$.)

good microscopic description of a healed opacity in a quiet eye. Opacities more characteristic of acute or chronic onchocerciasis were present in several whole eyeballs excised primarily for other reasons, but identification of individual ones is not easy. The microscopic appearances now to be described have been built up from all these sources of information.

It must be stated, however, at the outset that here is being presented a hypothetical sequence of events as to the course of punctate keratitis, each one of which in itself is accurate, but the order of the whole not necessarily so.

When a parasite finds its way below Bowman's membrane and dies there, it has already been shown in Section I that it attracts to the spot in great abundance several types of inflammatory cells such as the eosinophil leukocyte, the plasma cell and to a lesser degree the lymphocyte. When the parasite passes above Bowman's membrane, exactly the same sequence of events happens. There is nothing in this state of affairs which is likely to produce the minute discrete opacities typical of a classic punctate keratitis (as the photomicrographs show), nor has any other evidence been obtained which suggests it does.

The classic viral punctate keratides so commonly found in association with oncho-

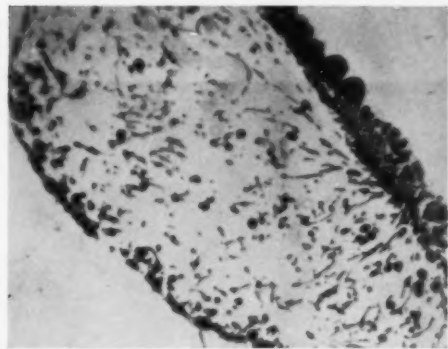


Fig. 44 (Rodger). Early migration of pigment from root of iris in acute anterior uveitis. (Masson, $\times 110$.)



Fig. 45 (Rodger). Established subacute anterior uveitis to show wide distribution of clump cells in stroma. (Masson, $\times 110$.)

cerciasis are those, it would seem, where the opacity is round and small; but there is nothing round and small in the collection of inflammatory cells discovered in the acute onchocercal eyes we examined, as serial sections well show. This supports the view that the punctate keratitis of onchocerciasis (in its acute stage particularly) only bears a superficial resemblance to the viral types, the

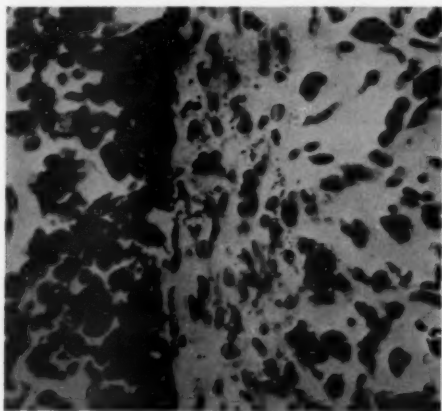


Fig. 46 (Rodger). Cushioning and clumping and scattered granules in severe anterior uveitis. Part of a microfilaria present (Masson, $\times 400$.)

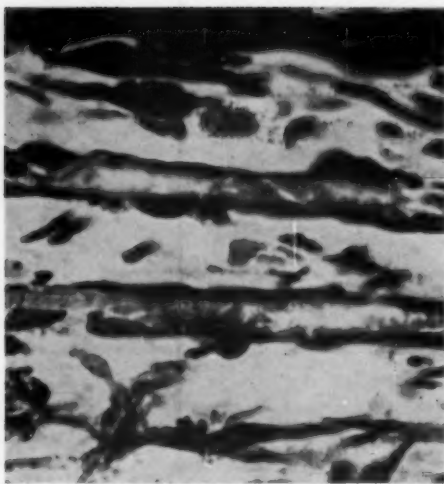


Fig. 47 (Rodger). Pigment mantles on iris capillaries in anterior uveitis. (Hematoxylin-eosin, $\times 500$.)

opacities being on the whole larger and denser as well as less round.

The large opacity formed around the dead parasite as it fragments during the acute phase of the keratitis will in the end either vanish into the advancing bulk of an associated pannus, when its individuality will go, or the nature of its infiltrate will change, and

the cells forming the opacity ultimately become absorbed. One would expect when the site is below Bowman's membrane that the accompanying fibrosis will leave a permanent scar, and alternatively, when above the membrane, that there will be no residuum. This is not the case, for an opacity clinically demonstrable as the latter has been found to depend on structural changes in the epithelium only.

Where, then, a parasite dies above Bowman's membrane, the early appearances are those due to the local aggregation of eosinophil leukocytes and the fragmenting body; the nature of the infiltrate then slowly changes until plasma cells displace the eosinophil; the close association of the toxins with the epithelium apparently causes it to atrophy; the cells become disordered and flattened; the nuclei are pyknotic and their alignment generally horizontal; PAS does not stain the muco-proteins of the basement membrane; pigment granules invade the cells at all levels, sitting like caps on the outer side of the nuclei, occupying the external part of the cell body. When the last of the inflammatory cells has become absorbed, it is these epithelial changes alone which persist.

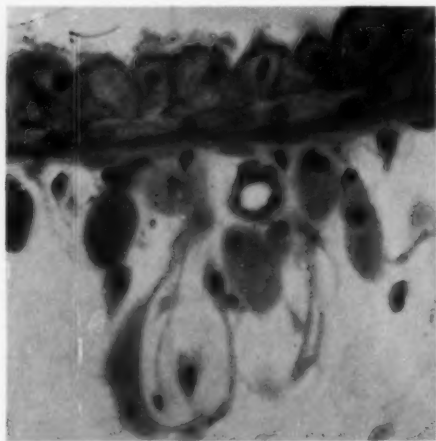


Fig. 48 (Rodger). Bleached melanoblasts of iris surrounding blood vessel in acute anterior uveitis, early stage. (Phloxine tartrazine, $\times 500$.)

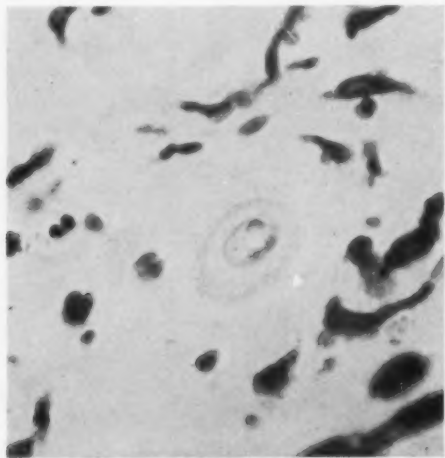


Fig. 49 (Rodger). Healthy iris blood vessel with characteristic space in wall. (Mallory, $\times 500$.)

If, on the other hand, the parasite dies in the stroma of the cornea below Bowman's membrane, although the changing nature of the inflammatory cells follows the same course, there is the extra complication of the stimulating effect the toxins have on the fibroblasts; being at a greater distance from the toxins (on the outer side of Bowman's membrane), the epithelial cells do not in this type become atrophic but are like the presumably tougher fibroblasts stimulated to proliferate. As a result the epithelium becomes hypertrophic, its nuclei staining darkly.

As for the basement membrane, it stains densely with PAS; it is thicker than normal and is disordered and granular. In the region of the parasite's supposed grave in the stroma, once the inflammatory cells have disappeared and the lesion quietened down, all that remains is an excessive collocation of disoriented collagen fibers which stain heavily with PAS; the hyperplastic epithelium lies directly above. Thus it is that persistent opacities can exist in the quiet eye both above and below Bowman's membrane, although



Fig. 51 (Rodger). Acute anterior uveitis, well established, showing swelling of vascular endothelium and reduplication of arterioles, as well as hyperactivity of pigment. (Masson, $\times 500$.)

unfortunately there is nothing specific in their appearance to distinguish them in the late stages from corneal opacities of other origin.

4. SCLEROSING KERATITIS

The essential changes here are those of repair, the dominant feature pannus forma-

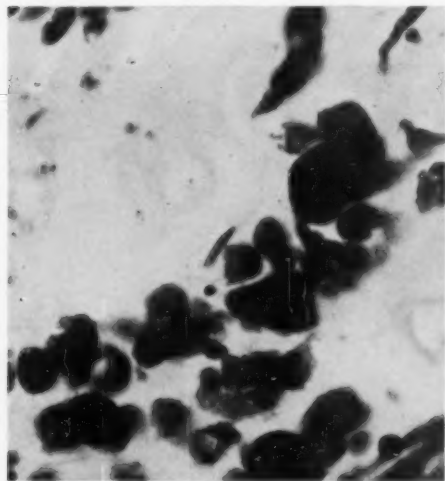


Fig. 50 (Rodger). Hyalinized blood vessels in advanced anterior uveitis and aggregation of pigment cells, the round granules of which can be made out. (Mallory, $\times 500$.)

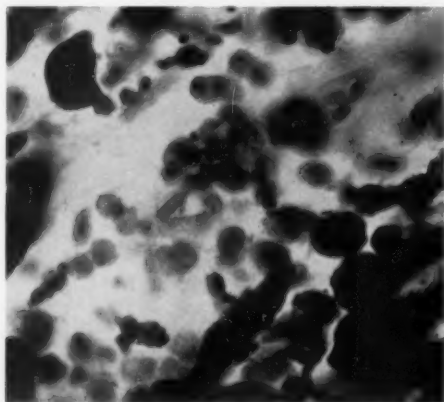


Fig. 52 (Rodger). Chronic anterior uveitis. Plasma cells dominate in the infiltrate. Also seen is an intracellular Russell body below. (Masson, $\times 500$.)

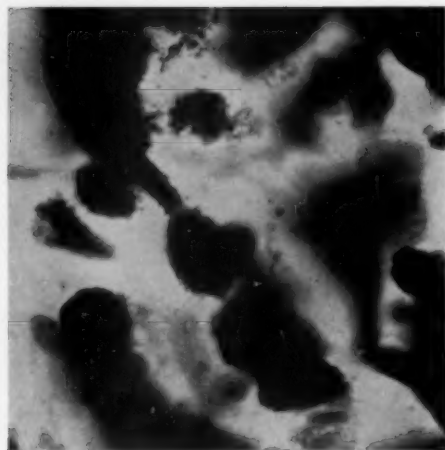


Fig. 53 (Rodger). High-power view of clump cells in iris shedding pigment granules and cushioning. (Mallory, $\times 860$.)

tion. In a transparent tissue like the cornea the damage results from the stimulating effect of the disease on the corneal fibroblasts. Loss of their transparency, it seems, depends not so much upon an alteration of the planes in which they lie as of their chemical nature.

The classic site of pannus onchocercosis is between Bowman's membrane and the epi-

thelium in the situation of pannus degenerativus. There is some disagreement about the constitution of the latter; some workers say it is rich in vessels and round cells, others that it has few or no vessels and is unassociated with inflammatory cells. Whatever the opinions held the pannus of onchocerciasis should never be confused with pannus degenerativus, as it is distinctive in character.

In advanced cases pannus onchocercosis is also found in the stroma; here it is in all respects identical with the pannus found above Bowman's membrane. The nature of the infiltrate distinguishes it from pannus eczematosis. Sometimes it advances far in toward the apex from the periphery, at other times it exists as islands in the stroma *apparently* isolated from the limbal vasculature, if that is possible. These interstitial patches are usually only 10 to 50 μ thick. The posterior third of the stroma was never found to be involved.

The keratitis of onchocerciasis may be associated with a punctate keratitis; it is always associated with a limbitis, marked congestion of the limbal vessels being a feature. The pannus never originates in the upper half of the cornea; it usually starts at the 3-

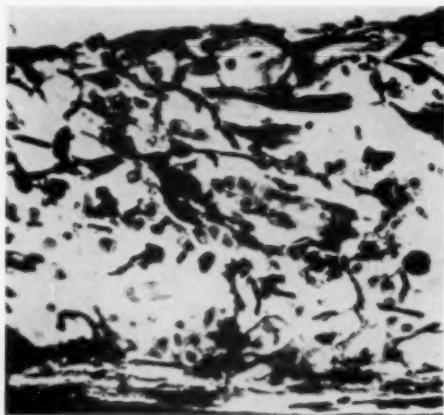


Fig. 54 (Rodger). Healing anterior uveitis, iris stroma shows persistent plasma cells, a single hyaline spherule, and signs of declumping of pigment. (Hematoxylin-eosin, $\times 260$.)

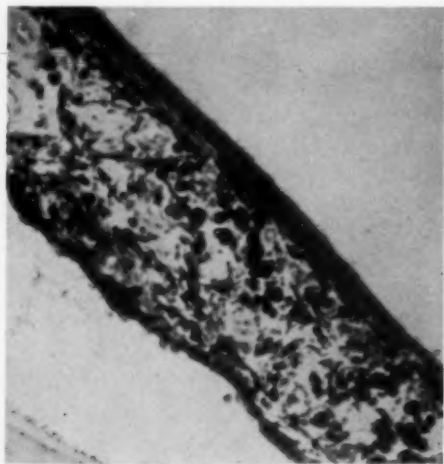


Fig. 55 (Rodger). Healed chronic anterior uveitis with decolorized pigment (Masson, $\times 110$.)

or 9-o'clock position in the form of invading tongues; sometimes it commences as an apron, advancing into the cornea from below toward its apex. Fusion of the tongues or of the tongues and apron, when both are present, is the rule, and ultimately leads to total opacification of the cornea. With the slitlamp a tongue of pannus consists of three zones as follows, reading from the limbus inward: a pigmented, a densely-white and a gray zone (Rodger¹⁵).

Microscopic appearance

The early changes in the cornea when a parasite dies therein have already been described in this thesis. Pannus formation is a development of the last phase mentioned there. Thereafter, when the characteristic sclerosing keratitis has commenced, new capillaries, fibroblasts, and inflammatory cells, of which plasma cells are most abundant and eosinophil leukocytes always present, can be seen.

The classic site of the pannus, as we have seen clinically, is above Bowman's membrane, although it may also exist below. This membrane does not seem to be readily destroyed; it is only in the more advanced cases that this

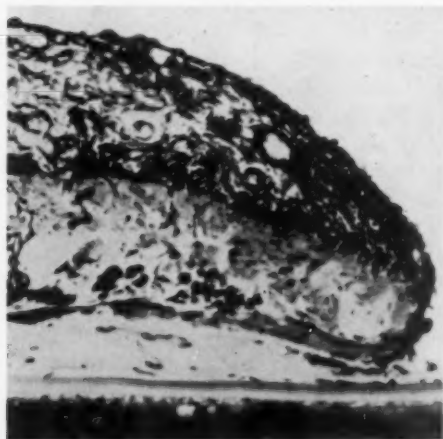


Fig. 56 (Rodger). Healed anterior uveitis, showing posterior synechia at pupillary margin. (Masson, $\times 180$.)



Fig. 57 (Rodger). Healed anterior uveitis with organized pupillary membrane. (Hematoxylin-eosin, $\times 110$.)

happens. It tends rather to be pushed out of the way, until the fibroblasts by force of numbers break it down and its continuity is lost.

The pannus pushes itself into the cornea in the shape of a wedge, so that its innermost advancing portion is the most thin. This explains the inner of the three zones, the gray, seen clinically, for here the optical density is least; above a certain thickness of pannus no light is transmitted at all and the color changes to white. This is the middle zone. The basal pigmented zone is so designated because the epithelium there takes up pigment. The distribution of the latter will be described later along with the epithelial changes.

The elastic fibers disappear throughout the stroma wherever it is involved in the inflammatory reaction; I have never been able to observe changes either in Descemet's membrane or in the stromal elastic tissue lying next it, although with distortions due to pan-



Fig. 58 (Rodger). Occlusio pupillae in old quiescent anterior uveitis. (Masson, $\times 80$.)

nus formation the former may seem to be changed clinically.

The epithelium of the cornea soon becomes hyperplastic and the nuclei stain more darkly above the area of pannus. Metaplasia follows until in the end early keratinization is seen. Pigment in the corneal epithelium exists at all levels in clear cells, but the greatest accumulation of it is to be found in the wing and basal cells, the granules occupying the outer halves of the cell bodies, as we saw in the conjunctiva. This hyperpigmentation appears to be a (melanoblastic) property of the resting epithelial cell rather than an invasion by chromatophores or the result of excessive production of melanin by known limbal melanoblasts. In long-standing cases epithelial pigmentation may be almost total.

As the keratitis advances into a chronic or

quiescent phase, the epithelial hypertrophy diminishes and atrophic thinning develops. The surface then becomes uneven because the processes of atrophy do not occur equally over the entire cornea. It is at this stage that Bowman's membrane usually fragments, and calcification of the membrane and the adjacent stroma commences.

In old cases of onchocercal endophthalmitis, epithelial bullae probably result from secondary glaucoma, almost certainly being due to pockets of fluid (keratitis bullosa or vesiculata) which later become filled in with fibrous tissue.

The vessels of the pannus persist for a very long time, the proliferating fibroblasts lying more or less parallel to them; it is the nature of the infiltrate which changes. In the early stages, as we have seen, eosinophil leukocytes are found among the plasma cells; earlier still, before pannus developed, the former were the dominant cells lying beside the disintegrating body of the parasite; they are the first to decrease.

In an advanced keratitis, therefore, the infiltrate consists of plasma cells, an occasional group of lymphocytes, plasma-cytoid cells in not inconsiderable numbers, and only a few eosinophil leukocytes; a good place to look first for the latter is in the congested blood vessels of the pannus along the periphery of the blood stream. No classic macrophage or giant cell was seen in the infiltrated tissue of the cornea nor were any Russell bodies found in this structure, although they are common in the uvea.

As in endemic areas repeated invasion of the eye is to be expected, so a complicated

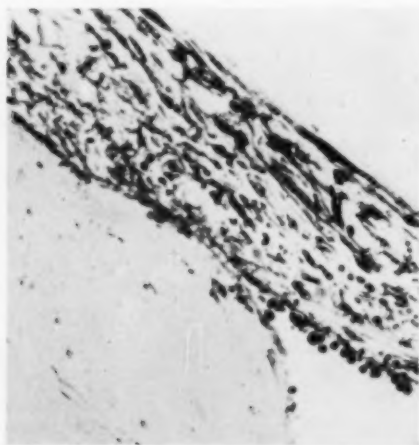


Fig. 59 (Rodger). Blockage of filtration angle in healed anterior uveitis. (Masson, $\times 110$.)

picture usually arises where acute and chronic changes overlap, and this may well explain why in long standing cases eosinophil leukocytes are still present; in healed areas, they might be expected to disappear if it were not for this. They never dominate the picture, however, as they do initially in the acute stage, except locally where a parasite in the early stages of dissolution exists.

As mentioned earlier, in association with this sclerosing keratitis there is marked congestion of the limbal vessels, which are invariably cuffed with plasma cells. As invasion of the eye by microfilariae via the limbal route is going on all the time, and as the life of the parasite is short, cuffing is to be expected. Here, too, fibroblastic repair is a feature, so that adhesions between the conjunctiva and the globe at the limbus are common. The internal elastic lamina of the limbal vessels becomes defective, and the scleral elasticum also stains badly. Parasite bodies are found in a heavily infected eye throughout all parts of the cornea in different stages of dissolution, and present a remarkable if somewhat confusing picture. I have found as many as 10 in one section (7.0μ) of cornea.

5. ANTERIOR UVEITIS

The microscopic appearances of the iris and ciliary body will be described under this single clinical term, although where there is onchocercal disease of these structures the anterior choroid is usually affected in consequence; in fact in severe cases the entire choroid will be affected, the condition being one of an endophthalmitis. Nevertheless, slight but authentic evidence was obtained that the posterior uvea can be attacked alone in the absence of anterior involvement, and so for this reason choroidal changes will be discussed separately under the heading of posterior uveitis.

The classic anterior uveitis of onchocerciasis exhibits occlusion of the pupil, frequent adhesions at the angle of the anterior chamber or at the posterior corneal face, and quite often a mass of tissue lying in the position

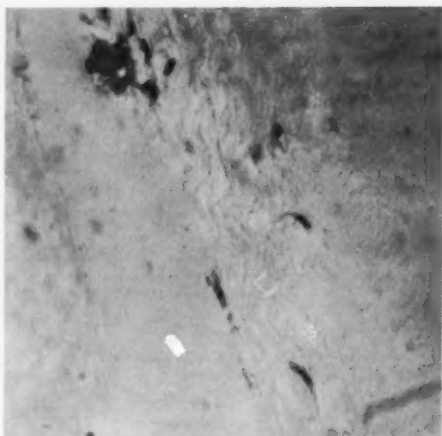


Fig. 60 (Rodger). Acute phase of anterior uveitis, showing exudate in anterior part of vitreous, as endophthalmitis develops, with amoeboid lymphocytes and monocytes present. (Hematoxylin-eosin, $\times 220$.)

one associates with hypopyon. In acute eyes these inflammatory exudates are soft and yellow, in long-standing cases they are tough, white and fibrinous. The latter lead to distortions of the pupil, characteristically in a downward direction so that it becomes pear-shaped. Where the occluding membrane becomes wholly or partially absorbed there is nothing specific in the clinical picture, so that it is harder to diagnose than, say, the keratitis. I think it is the acute phase which determines the prognosis; elsewhere (Rodger¹⁵) evidence has been presented that such acute attacks occur, although this hitherto had been denied.

The truth of the matter is that the course of the disease is punctuated by acute attacks of very short duration. If such an attack is severe, the inflammatory exudate will be great, and there is less chance of absorption occurring. The factors which determine the amount and degree of exudation are complex, and have been discussed in the previous part of this thesis.

When we take all these facts into consideration it is clear that to classify the lesion as either nongranulomatous or granuloma-

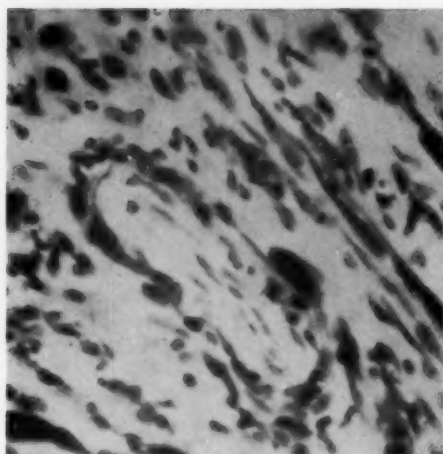


Fig. 61 (Rodger). Sclerosis of ciliary artery in anterior uveitis with chronic inflammatory cell infiltration of stroma. (Mallory, $\times 500$.)

tous is not possible; a short mild attack where the exudate is absorbed leaving few signs behind (characteristic of the former) is just as common as a long-standing one punctuated with acute phases which lead to occlusion or some other gross residuum (characteristic of the latter). In the description which now follows, the course of events is traced microscopically from the first acute attack to the resting phase in the old quiescent blind eye.

Microscopic appearance

If it is the extra-iridal exudate which dominates the clinical picture it should be the nature of the infiltrate within the tissue which dominates the microscopic picture—as it did in the case of the keratitis, where a high significance may be placed on the presence of eosinophil leukocytes beside disintegrating parasites. In fact, so dense is the pigment in the African uvea that there is no question that it is the pigment changes which are the most striking. We also found them the most interesting.

The toxic products of the microfilarial bodies lead to great activity on the part of the pigment cells. In the first instance, it is

those of the posterior pigment epithelium which are stimulated. Even in apparently healthy eyes a few of these cells can be seen to have broken away and passed into the iris stroma; usually they lie not far from the maternal epithelium, but some pass close to the anterior face of the iris.

Characteristic of the cell is the appearance which has been described as clumped. The clump cell, whether free or fixed, is the melanoblast of the iris.

The stimulus of the first parasitic toxins causes many of them to break away immediately into the iris stroma, a tendency most marked at the root; at the same time they step up the manufacture of pigment granules; these are shed into the tissues. I have never been able to see how the granules come to be liberated; the cell membrane does not seem to rupture; the granules appear to move out through the surface in a manner impossible to understand.

Whatever the mechanism, as the uveitis increases in intensity, vast numbers of these granules can be seen lying free in the stroma. In this way the second pigment cell of the iris, the chromatophore, comes into the picture.

Chromatophores can be seen at this time very actively reproducing themselves; mitotic figures are common, being more readily seen in the less dense chromatophore than in the very dark-colored clump cell. As soon as the chromatophore is formed it starts taking up the surplus granules. Clinically the lesion is still acute when the chromatophores themselves withdraw their processes and adopt the shape, if not the color, of the clump cell.

It seems probable that in the period between being released by the clump cell and picked up by the chromatophore the granules undergo a change, probably a chemical one; this would explain why their size is greater in the melanoblast than in the chromatophore. The lighter color and the smaller size always enable one to distinguish the latter from the former, even after each has become clumped.

Both cells tend to attach themselves to the walls of the blood vessels but, in view of the great proliferation of pigment cells and vessels, this may not be purposeful. I have found transitional forms between the amoeboid- and the clump-shaped chromatophore in acute eyes, so there is no doubt what is happening. Later on in the course of the uveitis they become increasingly dark in color until it is impossible to distinguish them from epithelial clump cells; one gets the impression, nevertheless, that the melanoblast always remains the larger.

In addition to the greatly increased activity of the epithelial clump cells within the stroma in raising the production of pigment (which makes one wonder "why?"), and of the chromatophores in multiplying and scavenging the granules, both types of cell gradually assemble along the anterior face of the iris; they also concentrate increasingly at the pupillary margin among and in the neighborhood of the inner circle capillaries and smooth muscle fibers. As a result of this activity in the acute and subacute stages the picture presented is of an iris bordered in black with a large polka-dot design within it.

In the established chronic anterior uveitis, the pigment epithelial cells which have migrated into the stroma have become so swollen that they now form what appears to be a continuous black band of pigment; in bleached sections they look like a line of compressed cushions; each of course is simply a fixed clump cell.

This is characteristic of a chronic anterior uveitis; in places several μ long, usually near the root whence the earliest and greatest migration occurred, the pigment epithelium is totally depigmented, and the few residual cells have atrophied. There is usually a membrane adherent posteriorly to the epithelium at these places, in the fibrin of which chronic inflammatory cells are entangled.

A similar cushioning occurs in the cells which have massed along the anterior face, although here the fused band of pigment is not so smooth in outline, nor is there any

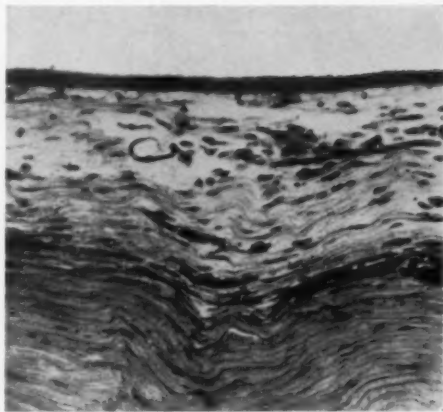


Fig. 62 (Rodger). *Microfilaria volvulus* in choroid. Early invasion of choroid following an anterior uveitis. (Masson, $\times 180$.)

evidence of depigmentation until much later. Clump cells of both types still abound in the stroma, but now in places there is usually evidence of a return to normality, for the processes of some of the chromatophores have started to reappear; the pigment within, however, is still dense.

When the processes of healing are complete and the eye becomes quiet, the most striking microscopic feature is the greatly decreased intensity of the pigment in the chromatophores. Once more they can be recognized by their elongated processes, but they are paler than in health and are compressed, lying parallel with the surface. The greater area covered now by these elongated cells as compared with the small spherical shapes when they were clumped gives them the appearance of sardines packed into the iris layer upon layer.

The row of pigment cells along the anterior face has become thin and in places depigmented, as happened earlier in the case of the posterior epithelium; the appearance of the latter is much the same. Here and there an occasional clump cell can still be seen in the stroma, its dark color in striking contrast to the other pale chromatophores, which helps to remind one of the inflammatory storm that has now subsided.

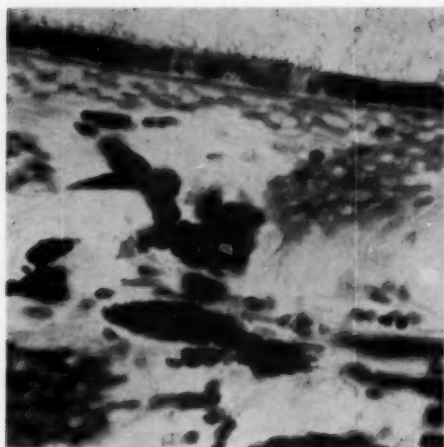


Fig. 63 (Rodger). Early signs of activity of retinal and choroidal pigment in posterior exudative uveitis. (Masson, $\times 220$.)

Many of the capillaries are heavily coated with pigment, the lumina often being occluded. There are no longer any signs of mitosis; no longer do surplus granules lie everywhere; no longer are collections of clump cells found in every available corner; one gets the impression that a wild party is

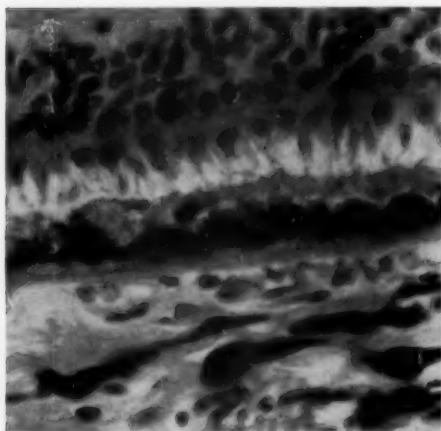


Fig. 64 (Rodger). Aggregation of retinal pigment and migration of choroidal forward into choriocapillaris in posterior exudative uveitis. The exudate can be seen above the pigment. (Masson, $\times 500$.)

over. Clinically the iris is faded and limp.

The description of the pigment changes in the iris should be supplemented by those in the ciliary body which are less dramatic but somewhat similar. The pigmented and the nonpigmented epithelium are both involved. There is some migration of the cells into the stroma of the processes, but not a great deal; the more usual route is on to the surface of the ciliary epithelium. Here the liberated granules lie in a cyclitic membrane where they are picked up and ingested by wandering cells. Local proliferation in places is associated, as in the case of the iris, with loss of pigment in others.

Subsequent to such complications as posterior synechias, where there has been gross proliferation and migration of pigment into the pupillary area, there is likely to result ectropion of the posterior epithelium or depigmentation of the fringe.

If the pigment changes strike the eye most readily, the vascular changes are almost as remarkable. In the early acute phase the vessels become heavily congested, the walls dilate, inflammatory cells—of which by far the greatest number are eosinophil leukocytes—can be seen lining the endothelial walls, and reduplication of vessels begins. The latter is most prominent at the inner pupillary mar-

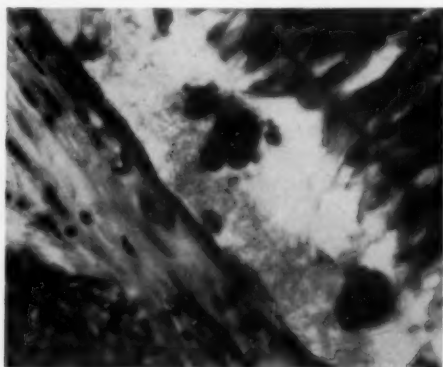


Fig. 65 (Rodger). Posterior uveitis. The cuticulum-secreting cells of the pigment epithelium are clearly seen where the pigment cells have broken away. Bruch's membrane is visible below, intact. (Masson, $\times 500$.)

gin, which swells to twice its resting size as a result.

When the anterior uveitis becomes established and passes from the subacute to chronic phase, the vessels begin to show evidence of poisoning. The endothelium swells and proliferates; the elastic lamina reduplicates itself but takes less and less stain. The ciliary vessels have an internal elastic lamina of the usual type, but in the iris it is never as clean-cut as elsewhere, even in healthy eyes; now, however, it stains very faintly if at all. The space normally present in the wall of the iris artery disappears as it is filled in with hyaline material.

In the ciliary body, on the other hand, fibrosis of the arteries not hyalinization occurs; this does no more than reflect the essential difference in the structure of the two vessels, which in turn reflects their different functions.

In old cases, where the uveitis is quiescent, these changes are even more striking: the lumen of the iris artery or arteriole is closed, a few heavily staining endothelial nuclei only remaining, and the rest of the vessel is hyalinized; no elastic fibers remain in the wall. In the case of the ciliary vessels many of them are completely sclerosed. The absence of vessels in the chronic anterior uveitis is

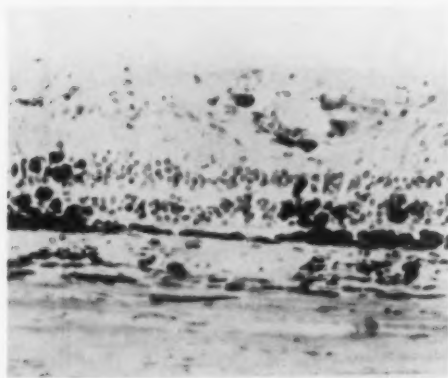


Fig. 66 (Rodger). Old healed case of posterior uveitis with migration of retinal pigment into retina and clumping of residual cells. The area has now been badly affected. (Phloxine tartrazine $\times 140$.)

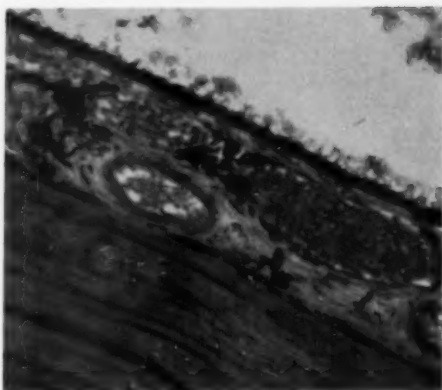


Fig. 67 (Rodger). Subacute phase of posterior uveitis with choroidal congestion, reduplications of vascular intima, and many eosinophils in the blood vessels. Much exudate lay over the ora in this eye. (Masson, $\times 220$.)

as striking as the abundance of them is in the acute.

The condition being described is characterized clinically by the exudate produced. In the early acute stages this exudate pours out from all the surfaces of the anterior uvea: into the anterior and posterior chambers, into the vitreous, over the ciliary processes and the pars plana, even above the anterior part of the retina; it also is present within the structures involved. As a result it covers the pupil, blocking the angle, forming posterior and anterior synechias, a cyclitic membrane and a suprachoroidal pellicle. Not surprisingly the health of the lens suffers so that secondary cataracts are extremely common.

From the start there is a lot of fibrin present in the exudate; even in eyes where the pathology suggests we are dealing with a chronic rather than an acute condition there is fibrin to be seen in the exudate. This supports the observation that repeated small acute attacks occur.

The exudate stains pale red with eosin, pale blue with the trichrome stains. The fibrin is less easily observed within the stroma of the iris and ciliary body. When the exudate is examined microscopically in the chambers of the eye, it is seen to contain

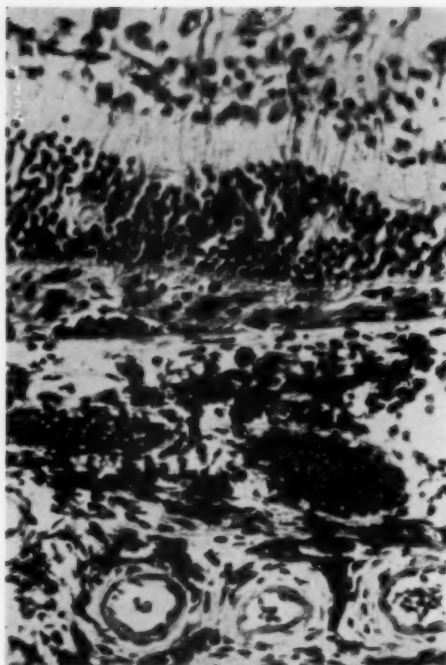


Fig. 68 (Rodger). Advanced stage in posterior exudative uveitis, with marked choroidal sclerosis, infiltration with plasma cells, a Russell body, and local breakup of whole retina associated with inward migration of the choroidal pigment. (Masson, $\times 220$.)

ghost cells (empty red corpuscles), fibroblasts, several plasma cells, a few lymphocytes and several monocytes. Only rarely was an eosinophil leukocyte found in the exudate of the ocular chambers.

In the advanced lesion the exudate has collected on the surfaces of the iris and the ciliary body. Fragments of parasites can be seen along with fibroblasts, plasma cells, lymphocytes (usually with a clearly outlined cytoplasm) and monocytes. The latter often show the elongated processes of an amoeboid phase.

The presence of monocytes in the free exudate is as striking as the absence of eosinophil leukocytes. An occasional hemoglobin body can be seen alongside the ghost cells and fibrin bodies may be found occasionally. Over the ciliary processes free pigment gran-

ules lie, some of them having already been ingested by monocytes.

In the healed condition organization of the exudate leads to the deformities already described, such as blockage of the angle with its resultant effect on intraocular pressure.

In the vitreous the residual exudate in the chronic stage is albuminous; there are many red cells and ghost cells present along with lymphocytes, plasma cells and monocytes, some of the latter being amoeboid, some round. The area occupied by the exudate, as we would expect, is now quite small.

Although the nature of the infiltrate *within* the iris and ciliary body is rather overclouded by the pigmentary and vascular changes, it is highly significant. In the acute eye there is a high proportion of eosinophil leukocytes. Some plasma cells also appear early. In the established lesion, subacute or chronic, plasma cells more and more dominate the picture, and plasma cytooid cells, Russell bodies both intracellular or free in the stroma, are common; the so-called unicellular Russell body, which we understand is the last stage in the process of degeneration of the plasma cell, is also found. Although present in both anterior uveal structures, the Russell bodies were much more common in the iris.

As the inflammatory reaction becomes quiescent the eosinophil almost completely disappears; the plasma cells, plasma-cytooid cells and Russell bodies which appear indicate what is happening. Rarely a small "nodule" of lymphocytes may be seen.

One new cell appears in the late stages, and that is a large acidophil cell with two or more nuclei, in the cytoplasm of which are several vacuoles and granules, some of the latter pigmented. Three or four such cells were invariably present in each half iris in each section, in chronic quiescent eyes. By reason of their size, four times that of a plasma cell, and the fact that their red cytoplasm was so distinct in the atrophic depigmented uvea, they are quite conspicuous. Clearly histiocytes, the size of these cells corresponds closely to that of a clump cell.

In my view it is probably a variant of the latter. This is a type of cell about the origin of which it is impossible to be dogmatic.

Such, then, are the changes which occur in the anterior uveitis of onchocerciasis. In brief, to collate the points which have been treated separately:

In the acute phase the pigment cells proliferate, the arteries and arterioles multiply, a fibrinous exudate in which red cells and inflammatory cells appear is poured out within and without the structures concerned, and in the interstitial tissue the dominant cell is the eosinophil.

As the condition settles into the chronic stage the pigment cells fuse into a solid band on both faces of the iris, the clump cells continue to multiply and get darker, the exudate starts to become organized, the vessels degenerate (the iris vessels becoming hyalinized), and the eosinophil leukocyte is replaced by the plasma cell. Russell bodies and hyaline spherules are now common.

After healing, when the eye is quiet (and blind usually), the pigment is pale, the iris chromatophores, thin and drawn out, lie parallel with the surface parts of the posterior epithelium including that covering the ciliary

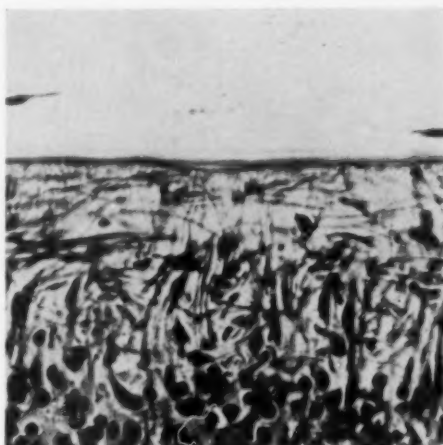


Fig. 70 (Rodger). Exudate on the surface of the retina in a posterior exudative uveitis showing fibroblasts. (Masson, $\times 280$.)

body and are depigmented; many vessels are hyalinized (in the iris) or sclerosed (in the ciliary body), deformities due to the organized exudate are common, and among the plasma cells which remain are found several large histiocytes intent on clearing up the debris.

6. POSTERIOR UVEITIS

The term posterior uveitis would seem to be a correct one, for it is an inflammation of the choroid, exogenous and exudative, due to the death of *O. volvulus* microfilariae in this structure.

Severe affections of the choroid always involve the retina, and in onchocerciasis this is no exception. I have never found a single case, however, where the retina was involved in the absence of choroidal inflammation, or where it was affected first, although the reverse is common. True, parasites have been found in the retina and, if they die there before dying in the choroid, a primary retinitis would ensue, but that I believe is a rare occurrence.

As a rule the retina is involved in the inflammatory reaction in small patches, a fact which can be observed macroscopically. It is possible that these areas of chorioretinitis occur only in the immediate vicinity of

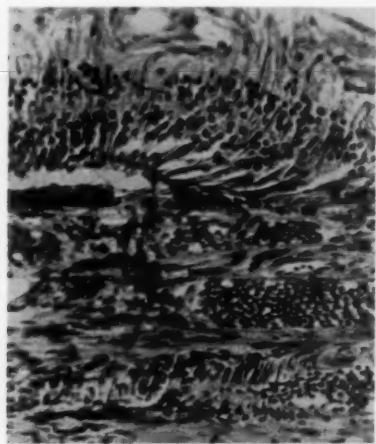


Fig. 69 (Rodger). The same eye as in Figure 68, adjacent. While the choriocapillaris is still patent, the overlying retina has started to degenerate over a portion of choroid that is badly affected. (Masson, $\times 220$.)

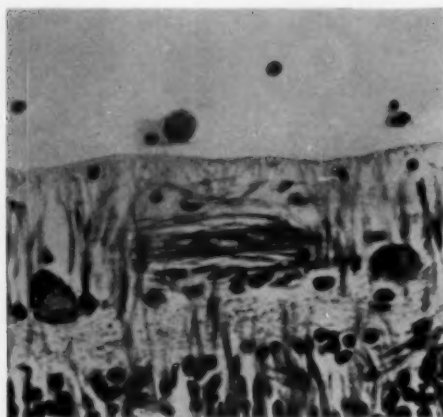


Fig. 71 (Rodger). The same picture as in Figure 70 in another eye, showing amoeboid lymphocytes and a macrophage. (Masson, $\times 280$.)

where a parasite has died in the choroid, the titer of toxin being sufficiently great at such places to affect the retina; the same products of intoxication on the other hand will spread readily in both directions within the choroid to enlarge the uveal lesion laterally.

It is difficult to explain how else these islands of chorioretinal fusion arise. With massive invasion, of course, the entire uveal tract and retina may be involved and there will be an endophthalmitis.

It has been mentioned that an anterior uveitis is usually associated with some de-

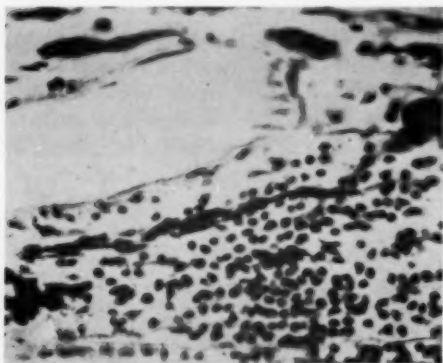


Fig. 72 (Rodger). Subacute posterior uveitis with a nodule of lymphocytes in the choroid. This is uncommon. (Masson, $\times 220$.)

gree of posterior inflammation. In early stages this may be due to the diffusion of toxins backward into the choroid; this would explain the presence of chronic inflammatory cells in the anterior choroid in the absence of microfilariae. Once the parasites have entered the iris and the ciliary body, however, they are almost certain to pass posteriorly into the choroid in the end, when a primary posterior uveitis will commence.

The cells characteristic of the new acute reaction will necessarily mingle with those of the subacute or chronic anterior inflammation, which has passed back earlier into the choroid. As a result it is as difficult to establish the existence of an acute phase in this lesion microscopically as it is clinically, where the fundus can seldom be clearly seen owing to the frequency with which the anterior segment is simultaneously involved.

Finally to be considered is the possibility of the posterior uvea being invaded by the parasites without anterior segmental invasion. This prospect was put forward clinically as a possibility in an earlier paper¹³; it was raised again when the passage of the microfilariae down the vascular sheaths of the equatorial vessels was described (Rod-

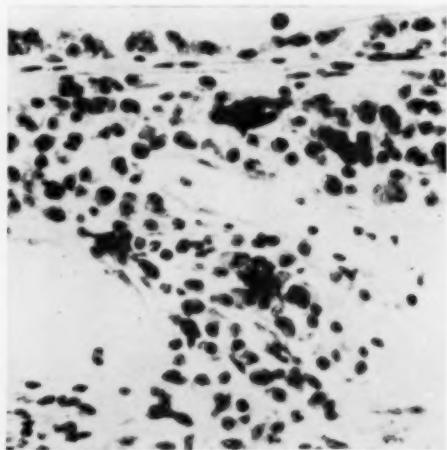


Fig. 73 (Rodger). Plasma cell infiltration is characteristic of the posterior uveitis (Mallory, $\times 220$.)

ger¹⁶); now one of the excised eyes furnishes proof of it. It is a nonspecific uveitis with which one is dealing, and may be confused at some stages with the degenerative lesion of the choroid and retina found in this same disease, which will be discussed next. Although there is no doubt that a primary posterior uveitis occurs, I hold to my previously expressed conclusion that such a lesion is seen very rarely as an isolated phenomenon.

In general, then, a posterior uveitis is associated with an anterior uveitis, the retina is involved secondarily and then only in patches, and it is rarely that a posterior uveitis is found by itself.

In some eyes with an anterior lesion a few chronic inflammatory cells are present in the posterior uvea, in others the uveal invasion by these cells is marked, in still others living parasites exist in the area that is infiltrated, and in others again living parasites are found outside the infiltrated area altogether, in what is apparently healthy choroid posterior to the equator.

These findings underline the chronologic and topographic chain of events leading

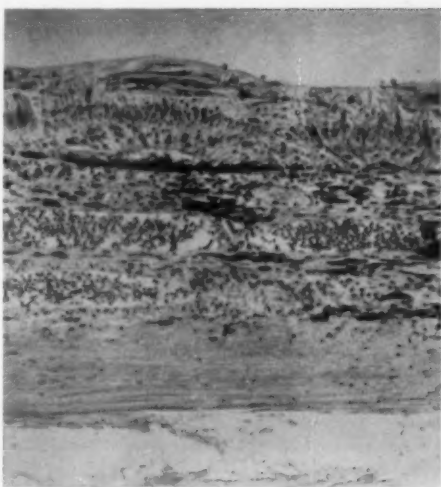


Fig. 75 (Rodger). Another section, showing the same as in Figure 74. (Mallory, $\times 90$.)

to the development of the posterior uveitis. Macroscopically the choroidal vessels are greatly congested, and the exudate coating the vitreous humor is noticeably present.

Microscopic appearance

The pigmentary changes although striking do not dominate the picture in the posterior

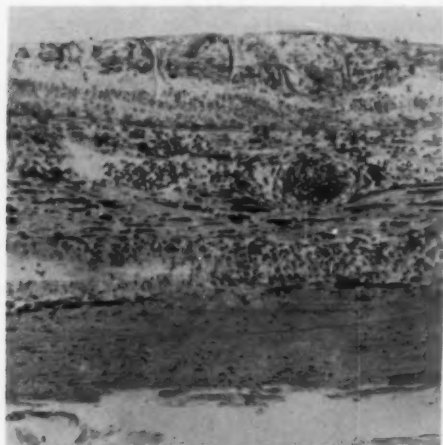


Fig. 74 (Rodger). Chronic posterior uveitis, showing patch of chorioretinal degeneration, with heavy infiltration of choroid by plasma cells and congestion of vessels. (Mallory, $\times 90$.)

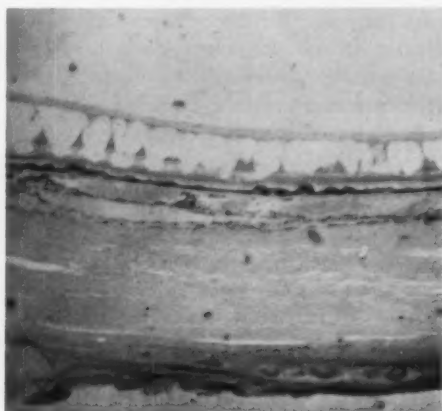


Fig. 76 (Rodger). Blessig-Iwanoff cysts and colloid bodies in old quiescent uveitis where both the anterior part of the choroid and the anterior uvea were affected. (Hematoxylin-eosin, $\times 110$.)

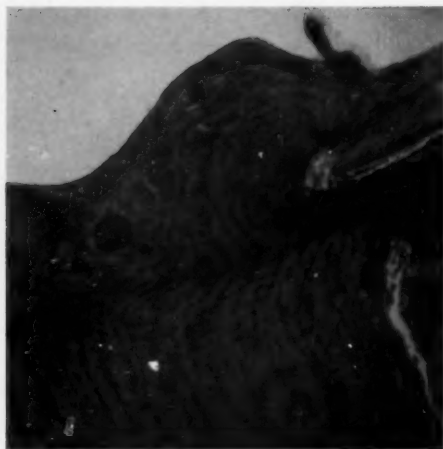


Fig. 77 (Rodger). Acute phase of posterior exudative uveitis, with great edema of the papilla. (Mallory, $\times 220$.)

uvea. In the Negro eye the choroidal pigment is darker than the retinal unlike the white races; the opposite state of affairs, as we saw, exists in the iris, where the pigment corresponding to the retinal (the posterior pigment epithelium) is darker than the pigment corresponding to the choroidal (the chromatophore of the iris stroma). This is important when the question of invasion of the retina by unidentified pigment arises.

At the height of the inflammation in the anterior uvea, both types of cell become equally dark; this is also true of the posterior segment. A second point of similarity

between the two areas is that the pigment granule formed by the retinal melanoblast is bigger than the granule contained in the choroidal.

These facts do not seem to have been reported before; nor do they correspond to what has been described in the European eye. As the retinal pigment is affected early on in an onchocercal uveitis they will be described along with those occurring in the choroid.

The granules of retinal pigment are characteristically spindle-shaped. They lie within the outer processes of the rods and cones, the base of the epithelial cell being devoid of pigment in its outer part; the granules, present in its inner part, are more elliptical than those in the processes, but are not completely round as some writers have said.

The nuclei of the retinal pigment epithelium are of two types, suggesting that two types of cell are present; one is darker and flatter than the other. It is believed that the former manufactures the inner cuticular layer of the membrane of Bruch, while the other type of cell with the paler, rounder nucleus is concerned wholly with the manufacture of pigment. The changes which develop consequent on the death of parasites in the uvea support this view.

Taking the posterior segment of the eye as a whole, disruption of the retinal pigment epithelium occurs only adjacent to an inflammatory focus in the choroid. This is an im-



Fig. 78 (Rodger). Posterior exudative uveitis, now healed, exhibiting long area of chorioretinal destruction at the posterior pole. This is the stage which resembles the degenerative lesion most. (Masson, $\times 30$.)

portant means of distinguishing between the exudative posterior lesion and the degenerative one.

Coinciding with the reaction of the retinal pigment is that of the choroidal; here the uvea is affected over broader stretches and disturbance of the pigment can be seen in all parts.

The first change observed was that the spindles of pigment in the processes of the retinal pigment cells withdrew from between the outer limbs of the rods and cones into the cell body, mixing with those already there. As they do so they themselves become rounder, corresponding to the granules already there.

At first sight these changes seem to occur in every cell in that area but, as they become clumped under further provocation and break away into the retina, the second type of cell, that with the flatter darker nucleus, becomes exposed. The latter are now visible as a single continuous layer of flat cells, maintaining in some way the continuity of the epithelium despite the breaks made by the pigment cells which have broken away.

The clump cells of the retinal pigment do not wander far during the initial acute phase, usually being found lying nearby between the rods and cones. They tend to form small groups, attaching themselves to each other.

The choroidal pigment cells, meanwhile, have moved imperceptibly inward toward

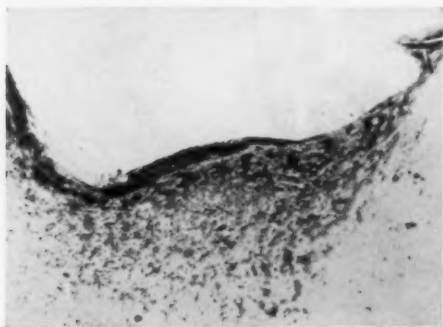


Fig. 79 (Rodger). Old chronic onchocercal anterior uveitis, with some involvement of the choroid as well, which has led to secondary glaucoma. Deep cupping of the disc. (Masson, $\times 120$.)

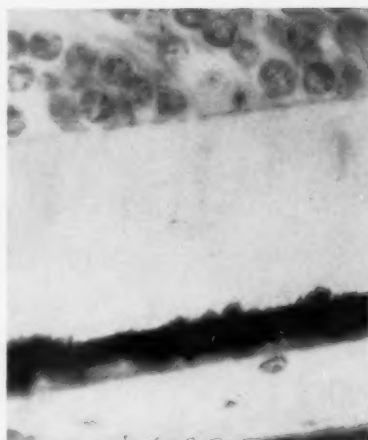


Fig. 80 (Rodger). Normal appearance of retinal pigment granules. The rods and cones are out of focus. (Phloxine tartrazine, $\times 1000$.)

the choriocapillaris, which is pigment-free even in the negroid eye. These cells are so dark that it is difficult to assess the relative size of the granules except at the periphery.

As was seen in the anterior segment, the granules leave the clump cells of the retina without apparently breaking the cell body, but none apparently is liberated outward into the choroid. The membrane of Bruch probably prevents it.

The increase in density of the uveal pigment posteriorly, therefore, would appear to depend upon the tendency of the choroidal pigment cells to make more pigment and accumulate in masses rather than on taking up surplus granules released by the retinal cells.

As the condition advances the retinal pigment also gets darker until the color corresponds to the very dark choroidal pigment. At this stage, unless the size of the granules can be assessed, there is no way of concluding by this means whether or not choroidal pigment has passed into the retina. In fact it never does because, although the continuity of the cuticular lamina of the membrane of Bruch is broken in severe cases, the elastic lamina never is—not even in an onchocercal endophthalmitis.

In long-outstanding cases the cuticular

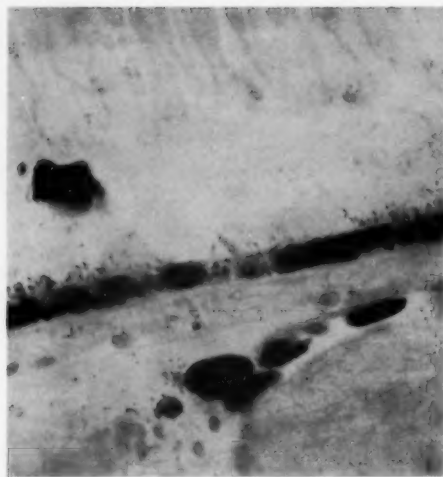


Fig. 81 (Rodger). First changes in the posterior degenerative lesion—retinal depigmentation giving rise to term "freckling of the fundus." (Mallory, $\times 500$.)

layer becomes locally hyalinized with the production of colloid bodies. In addition, the retinal clump cells migrate into the nervous layers above, and in places the vessels are surrounded by pigment granules, which either have been liberated by the cells or left behind when the pigment cells disintegrated.

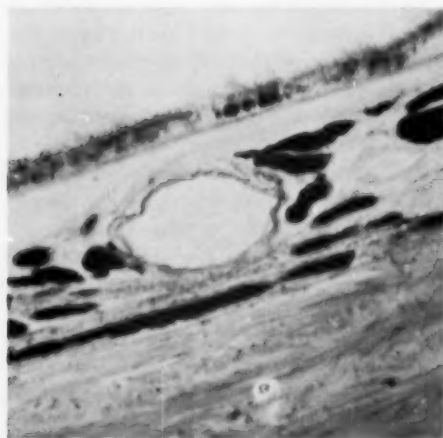


Fig. 82 (Rodger). Here the depigmentation of the retinal pigment epithelium is even greater. (Van Gieson-Weigert, $\times 500$.)

The distribution of pigment around the retinal vessels is dissimilar to that observed in retinitis pigmentosa; it does not attach itself by preference to veins, but to arteries, and lies indiscriminately among the ectodermal glia and mesodermal adventitia, forming large plaques of pigment, seldom seen with the ophthalmoscope, in the shape of bone corpuscles.

When the eye becomes quiet, the choroidal pigment cells start to elongate, as we saw in the iris, and lie parallel with the membrane of Bruch; they retain their dark color and tendency to stay close together. The part of the choroid corresponding to Haller's layer of vessels is frequently now devoid of pigment cells. The retinal pigment is most frequently seen at this stage in small rounded aggregations lying among the rods and cones. These changes are most striking where the greatest infiltration and destruction of tissues has occurred in the choroid. Such areas are disseminated although sometimes confluent as well.

The inflammatory exudate of the posterior uveitis is found within the choroid, between the choroid and the retina (in places), and on

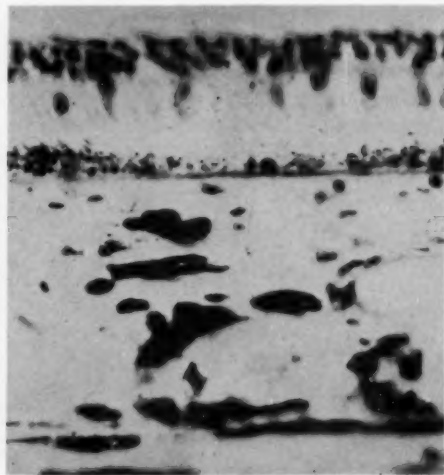


Fig. 83 (Rodger). A still more advanced stage of retinal depigmentation, still with no sign of clumping. (Masson, $\times 440$.)

the surface of the retina. It is acidophil with much fibrin in it until the chronic stages are reached. The same types of inflammatory cell can be seen in this condition as were described in the anterior uveitis; eosinophil leukocytes early dominate, later plasma cells. Plasma-cytoid cells and Russell bodies are not uncommon but we never found large histiocytes as we did in the iris.

The vascular changes also reflect those found anteriorly, and in a structure like the choroid are of course important. Early the endothelium of the congested vessels become swollen. Eosinophil leukocytes are present in large numbers in the paraxial stream. The endothelial cells then proliferate both in arteries and veins, especially the former. Hyperplasia of the media and adventitia commences until the process of sclerosis leads to complete occlusion. The internal elastic lamina of the arteries is not affected until late when it stains faintly or not at all. The choriocapillaris is not affected first; even in chronic cases it is patent except where the greatest destruction has occurred. Sclerosis when present is striking but is by no means widespread.

In the vicinity of the greatest destruction of the uveal tissue, probably the site of a parasite's death, the retina is grossly affected. Where a parasite dies within the retina such destruction would be greater still.



Fig. 84 (Rodger). Healthy macula in early case of degenerative lesion. (Masson, $\times 55$.)

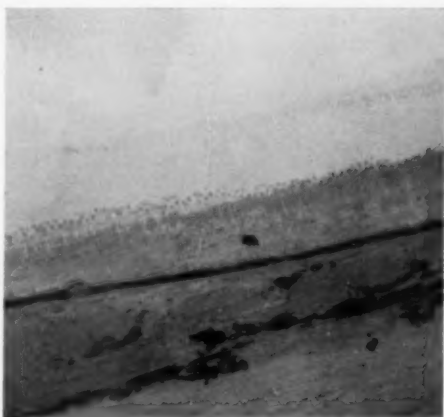


Fig. 85 (Rodger). Affected macula, pigmentary changes and edema, in another early case of the degenerative lesion. (Hematoxylin-eosin, $\times 110$.)

The rods and cones in these areas are quickly destroyed by the toxins, the bipolar cells diminish in number, the ganglion cells become distorted, and finally, in this order, the rod and cone granules (which appear to be the most resistant of all) become reduced.

Gliosis occurs in the later stages. Thus when the lesion has healed, a gliosed retinal

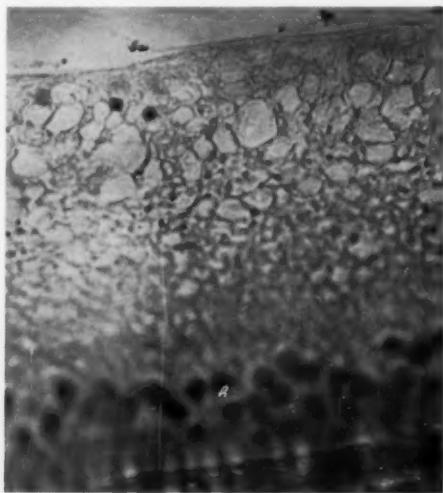


Fig. 86 (Rodger). High-power view of the macular edema in the case shown in Figure 85. (Hematoxylin-eosin, $\times 500$.)



Fig. 87 (Rodger). Edge of the degenerative lesion, showing disappearance of rods and cones and their nuclei, loss of retinal pigment, and very slight plasma cell infiltration. (Van Gieson, $\times 110$.)

patch lies side by side with a fibrosed choroidal. This has, in my opinion, been wrongly described as an area of chorioretinal fusion. There is no actual fusion, for even in the most severely affected areas, as has been pointed out, the membrane of Bruch remains intact. The plasma cells in the uvea which are present for a long time in such areas,

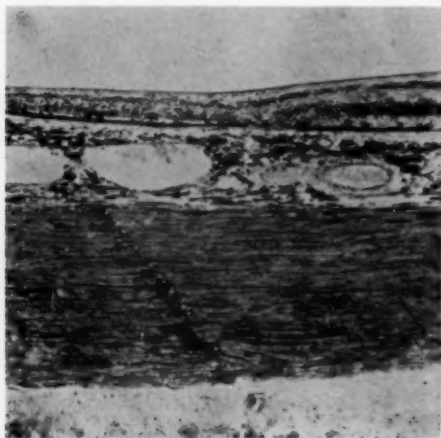


Fig. 88 (Rodger). The same type of case as in Figure 87, showing aggregation of retinal pigment at punched-out edge of the degenerative area. Choroidal pigment has moved inward. There is sclerosis of the choroidal artery on the right, and very little infiltration considering the destruction. (Van Gieson, $\times 110$.)

resemble the rod and cone granules, giving the impression that the latter have invaded the choroid; this may have encouraged the idea that actual fusion occurs.

What is essentially a nonspecific posterior uveitis has been described. It is the association of such a condition with anterior segmental lesions typical of onchocerciasis which establishes the diagnosis. *I have, nevertheless, at no time failed to find in such eyes living or dead microfilariae in the choroid.*

7. THE POSTERIOR DEGENERATIVE LESION OF ONCHOCERCIASIS

It was first suggested by me that this condition is a degenerative one, not an inflammatory (Rodger¹⁷). When coupled with the observation that an (inflammatory) posterior uveitis also occurs in onchocerciasis much of the confusion which has ruled in the past can be eliminated (Rodger¹⁸). The fact of the matter is that ever since an affection of the choroid and retina in this disease was recognized by Bryant¹⁹ and Hissette,²⁰ the posterior segmental changes have



Fig. 89 (Rodger). High-power view in middle of degenerate area, showing few plasma cells, overgrowth of choroid with fibrous tissue, total disappearance of choriocapillaris and the arteries, and persistence of the membrane of Bruch above. (Mason, $\times 250$.)

been a controversial topic; while I have established without doubt that microfilariae die in the posterior uvea and produce an inflammatory condition there, which may or may not involve the retina, the pathogenesis of the degenerative lesion has not yet been explained satisfactorily. An earlier part of this thesis attempts to do so. The important thing to remember is that the degenerative lesion is *not* associated with the presence of parasites in the eye, yet is only found in onchocerciasis patients.

The fact that so vague a descriptive term should be given to the lesion might appear to underline a certain lack of confidence on my part in the pathogenesis I have suggested. This is not true. In classifying it one is up against a difficulty inherent in ophthalmology, the classification of which includes many misnomers that remain unchanged because they become colloquialisms.

The most common error has been in classifying a disease as inflammatory when it is in fact not associated with any of the phenomena of inflammation. The usual alternative has been to rename these nosologically incorrect terms as "pathies" or degenerations, although these may be heterogeneous groups based on inconsistent criteria.

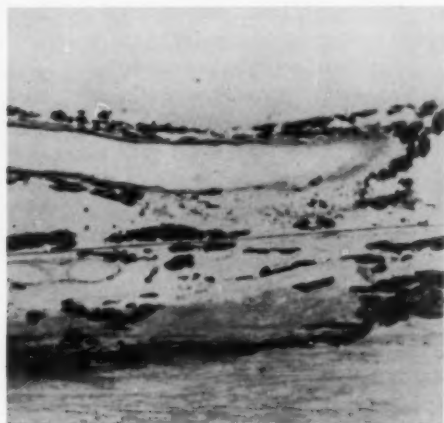


Fig. 90 (Rodger). Pigment mantle in a retinal artery in posterior degenerative lesion, exhibiting peripheral corpusculations. (Weigert's elastin stain, $\times 110$.)

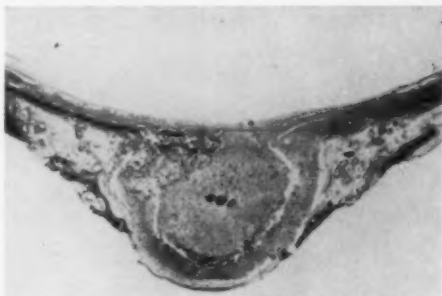


Fig. 91 (Rodger). The posterior degenerative lesion of onchocerciasis. This low-power view reveals the clearly demarcated edge of the lesion on each side of the disc, and the uniformity of the destruction within it. (Mallory, $\times 30$.)

The lesion in question could be described as an atrophy, but is it an atrophy? Do atrophy and degeneration clinically mean different things? Atrophy may occur as a result of the action of toxins, I know, and in this lesion I have suggested intoxication plays a part, which might lead to arterial spasm or to vascular degeneration and atrophy of the rods and cones.

Avitaminosis A may also play a part, and the word atrophy scarcely covers that; degeneration would be better.

Then again I may be wrong on all counts. There may be some explanation other than an intoxication coupled with vitamin-A deficiency. The lesion might be classified as a disorder of metabolism, or of circulation, or even turn full-circle and prove to be a mild inflammation after all.

In ophthalmology each of these possibilities would determine the ultimate title; so it has been called simply "the posterior degenerative lesion of onchocerciasis," leaving it for other workers to confirm or disprove the proposals as to the pathogenesis before being committed to anything more definite.

Clinically, one would be justified in calling the condition a central areolar circumscribed choroidoretinal atrophy, for that is what it looks like. Such conditions may be familial in origin, but this explanation has been eschewed because in a primitive community it can never be proved. My experiences suggest



Fig. 92 (Rodger). Early atrophy of the optic nerve in the degenerative lesion. (Mallory. $\times 200$.)

that inbreeding in the endemic onchocerciasis areas of Africa is a myth encouraged only by the more flamboyant of the anthropologists and sociologists, who crowd there from the west. Familial lesions are rare.

In the condition being described, there is no exudate, little infiltration, no sign of eosinophilia, no parasite in the eye, no anterior onchocercal lesion with which to tie it in (except rarely and then as a secondary complication). There are no areas of choroidoretinal inflammation disseminated here and there, just a simple straight-forward atrophy of the retina and the choroid, all of one piece, with a clear-cut margin, within which, as a result of pigmentary degeneration, the choroidal vessels can be seen. It is strange the two conditions have been confused for so long, yet, although the difference between them is so obvious microscopically, clinically pigmentary upset and exposure of choroidal vessels dominate each.

Microscopic appearance

The earliest changes (if not the most striking) involve the retinal pigment epithelium and the choriocapillaris. Neither of them coincide topographically, so it is impossible to say which occurs first, and it is unlikely that one causes the other.

The first area affected usually lies between the disc and the macula, although in some eyes the changes are observed simultane-

ously in both parts. A reduction of the number of patent loops in the choriocapillaris is not so commonly seen at an early stage as the pigmentary disturbance, but is the rule in the area next the papilla.

The changes in the retinal pigment are those of depigmentation. The thinning-out process is best likened to the effect that would be produced if every second stake in a fence were removed. This corresponds to what I have described with the ophthalmoscope as "freckling of the fundus." It is a genuine loss of color for the outline of the spindle-shaped granules can be seen devoid of pigment; as a result the choroidal vessels can early be viewed with the ophthalmoscope, although at first they will be healthy. The macula, which may or may not illustrate these changes is usually edematous; the latter vanishes later on when the macula becomes increasingly involved in the atrophic processes.

In the established case where there is no longer any doubt clinically as to the diagnosis, certain areas of the retina reveal proliferation of the pigment cells; they become clumped and either fuse together into a long thick band of pigment (usually at the periphery of the lesion) or break away into the nervous layers of the retina where they form small aggregations or even attach themselves round the retinal vessels. Here, too, nevertheless, colorless granules can be seen.

Secondary "retinitis pigmentosa" occurs in five percent of all posterior cases. It is a term that is open to error. I have never seen the fine bone corpuscle appearance typical of a primary retinitis pigmentosa, nor does the distribution of the pigment around the vessels correspond. It is usually much darker and more clumped, and for this reason the term "pigment corpusculatation" is preferred; it can be modified by adjectives to suit all occasions.

Around the vessels, the swollen pigment cells lie in all three coats of the arteries up to and touching the internal elastic lamina; nor are hyaline changes in the smaller vessels seen as in primary retinitis pigmentosa; and

the choriocapillaris is always affected somewhere. In none of these respects is the posterior lesion similar to a familial retinitis pigmentosa.

The reaction of the retinal pigment epithelium has been described at length for it seems to be of the highest importance, coinciding clinically, as it does, with hemeralopia.

The changes in the choroidal pigment are less marked; the cells tend to migrate into the pigment-free choriocapillaris, but they do not aggregate very much, which was a feature of onchocercal uveitis; even in the areas of worst degeneration it is found in small patches, distributed equally throughout this structure, each patch consisting of two or three sausage-shaped cells strung together, and parallel with the surface.

Wolff²¹ calls them both chromatophore and melanoblast, which is a contradiction in terms at first sight. Yet there is no way of explaining, as was done in the case of the iris, how the choroid cells obtain the pigment. The nearest melanoblasts are in the retina separated by the impervious lamina vitrea as was shown when the inflammatory lesion was described. Wolff is almost certainly right, for in the degenerative type the elastic lamina of Bruch always stains well. It is a complete barrier between the two cells.

Coinciding with the retinal and choroidal pigmentary disturbances just described is a striking degeneration of the retina. The rods and cones are totally destroyed and their attached nuclei disappear. The bipolar cells become reduced in number, and some fall out of line. They never completely disappear, being the only survivors. The ganglion cells degenerate imperceptibly, and there is no gliosis; the retina simply dissolves away, figuratively speaking.

The affected area commences abruptly with the sudden disappearance of the rods, cones and their nuclei. This gives the lesion its characteristic punched-out appearance. As one approaches the disc, all that remains in what is the oldest part of the lesion is a

thin layer of bipolar cells, two cells thick very often. The same appearance is found on the other side of the disc (for this is an areolar lesion).

As one moves away from the optic nerve-head one finally comes to the same raised margin, as healthy retina appears once again. This margin is frequently accentuated microscopically (concealed clinically) by a heaping-up of the retinal pigment cells, which become very dark and expanded. The membrane of Bruch over the entire area maintains its continuity; nor have I ever seen infiltration of the retina with chronic inflammatory cells.

The choroidal changes which coincide are equally distinctive. There is no congestion of the vessels, no exudate, and the marked hyperplasia of all the coats of the arteries, as well as the elastic changes in the vessel walls seen in the exudative lesion, is absent; moreover infiltration with plasma cells is only half as great.

The fibrocytes, which constitute the adventitial sheaths and the syncytium of the stroma in which the vessels lie, insidiously overgrow the choriocapillaris, arterioles, and arteries of the posterior uvea. The veins which for the greater part lie in the outer side of the choroid do not seem to be so greatly involved.

It appears that what we are dealing with is a reactive fibrosis of a very slow and subtle type. This is the sort of thing which could happen as a result of an ischemia from prolonged arterial spasm, like that caused by an intoxicant. A cursory glance gives the impression that no sclerosis of vessels exists, for none of the whorled vessels typical of arteriosclerosis is to be seen.

It is only on closer inspection that one becomes aware that not only has the choriocapillaris completely disappeared in the degenerated area but that most of the arteries have as well. Earlier we have noted some hyperplasia of the intimal coat, but now the intima is not to be seen; the elastic lamina is also lost. There are no monocytes or giant

cells in the established case but plasma-cytoid cells, lymphocytes and an occasional Russell body may be found among the plasma cells; the lymphocytes rarely collect into fairly large "nodules."

The final question to be answered is whether or not the retinal degeneration occurs as a result of a choroidal sclerosis. The pigment changes and the rod and cone degeneration, however, are not necessarily associated with an overlying sclerosis of the choriocapillaris, so we tend to the view that the two are not at first any way related. When the blood supply of the choroid, however, becomes seriously reduced, then probably the whole retina is quickly involved. The comparative resistance of the bipolar cells must depend upon the nutrition obtained from the retinal vessels themselves.

8. OPTIC ATROPHY

At a meeting of the Royal Society of Tropical Medicine and Hygiene in London in January, 1958, when onchocerciasis was discussed, the following statements were made:

1. Iritis does not cause cataract.
2. Optic atrophy and retinal degeneration are not manifestations of onchocerciasis.
3. As *O. volvulus* microfilariae are not found in the blood stream, it is difficult to understand how they gain access to the optic nerve and the choroid.
4. Onchocerciasis is not a serious cause of blindness.

It is a good thing for the fair name of the eminent society concerned that most of the speakers did not agree with these wild statements. The present thesis supplies most of the answers, which had been suspected by field workers in many instances, and in others already known and recognized.

Optic atrophy, nevertheless, is one condition which we agree is doubtful. Workers, such as Toulant²² with whom I have had long discussions, consider that onchocerciasis produces a characteristic optic atrophy which may be recognized by sheathing of the arter-

ies; there is nothing more to their arguments than this, which seem rather slender.

No eye where an isolated optic atrophy existed was examined microscopically in the present studies, so there is no new evidence to confirm or disprove that a primary optic atrophy can occur as a result of this disease. On epidemiologic grounds I have shown elsewhere (Rodger²³) that it is unlikely. On pathologic grounds I have also shown that it is unlikely, in Section I of this part of the thesis. However, in a heavily infected eye, there is no doubt that the optic nerve can be and is invaded. Giaquinto has also shown microfilariae in the nerve substance, as previously mentioned.⁹

In a posterior uveitis and in the posterior degenerative lesion, atrophy of the nerve is certain to happen sooner or later as a secondary phenomenon; where the parasites in the former condition pass into and die in the nerve itself, then the lesion will in a sense be a primary inflammation. Whether this happens in the absence of other lesions in the eye, I cannot say but I doubt it.

Atrophic cupping is the rule in the case of the posterior degenerative lesion, but in the uveitis, where anterior and posterior lesions are frequently conjoined, glaucomatous cupping is common, the angle of the eye being blocked by the organized exudate. Sheathing at the disc is variable, and in my opinion occurs more often in the inflammatory than in the degenerative lesion. The microscopic appearance confirms most of these generalizations.

Microscopic appearance

In the early stages of the posterior uveitis the nervehead does not appear to be affected. In an established (acute to subacute) case there is definite edema of all the tissues of the papilla. It even involves the adjacent retina. The swollen disc protrudes into the vitreous; this is not accompanied by very much infiltration with inflammatory cells, although the retinal and posterior ciliary vessels show an unusually high proportion of

eosinophil leukocytes then. In addition all the vascular coats exhibit signs of hyperplasia at a fairly early stage in the condition, and within the nerve itself the nutrient vessels are engorged.

Later, in the chronic stage, there is dense infiltration of the septa and papilla with plasma cells, lymphocytes and several eosinophils, the former of which are widely distributed. They can even be seen lying on the surface of the disc in a pellicle of fibroglial tissue which has formed there around the roots of the vessels; they are the dominant cells in perivascular infiltration of the small vessels making up part of the circle of Zinn. The melanoblasts of the retina and the pigment cells of the choroid now migrate and accumulate at the edge of the disc usually above the level of the lamina cribrosa. In one eye we found them forming a mantle around a retinal vein. Early gliosis has also commenced, and it is noticeable that it is the paler of the glial nuclei which is involved in proliferation. The edema, so prominent earlier, at this stage is gone.

In the healed quiescent posterior uveitis, glaucomatous cupping is the first thing to meet the eye, the lesion being usually associated with an anterior one. The septal vessels have become largely sclerosed as to a certain extent have the retinal and posterior ciliary arteries. The nerve fibers are atrophic and the process of gliosis now heavily involves the nerve proper as well as the adjacent retina.

In the posterior degenerative lesion the picture is quite different. The disc has never been found edematous, nor has glaucomatous cupping been seen; an atrophic cupping is more likely to be present. Eosinophil leukocytes at all stages are conspicuous by their absence, not even being seen within the lumen of the vessels, which is a useful way of spotting them quickly. Sclerosis of the retinal and posterior ciliary arteries does not seem to occur. In advanced cases there is a slight to moderate infiltration with plasma cells. The nerve itself when the condition is ad-



Fig. 93 (Rodger). Old case of degenerative lesion, with atrophic cupping of the disc. (Hematoxylin-eosin, $\times 220$.)

vanced becomes atrophic and gliosed to such an extent that the septal vessels have largely disappeared. While the choroidal pigment may be somewhat heaped at the disc margin, more usually it is not. As for the retinal pigment adjacent to the tissue it is among the first to become colorless.

From these pathologic observations, it would seem that the appearance of the optic nerve should be of great importance in the clinical diagnosis of a posterior lesion, especially in early cases. However, early cases are rarely seen, so, although it has been reported, I have never witnessed a papillitis. The optic nervehead undoubtedly is more useful in indicating which of the two posterior lesions is being dealt with in advanced cases. It is doubtful if either a papillitis or an optic atrophy ever occurs apart from a co-existing posterior lesion. After all on what grounds could such primary conditions be diagnosed as being due to onchocerciasis where found alone? The picture is quite non-specific.

But this is dangerous ground on which we are treading; that the optic nerve in onchocerciasis can exhibit a papillitis or an atrophy has been demonstrated, although in every case apparently secondary to a co-existing lesion in the posterior uvea and retina; theoretically a primary affection could also occur. That has to be admitted.

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PART V: CONCLUDING

The names of Ochoterena,¹ Strong,² Hissette,^{3,4} and Rodhain⁵ are among the most renowned in the history of the pathology of onchocerciasis. Of British workers, Bryant⁶ reported on two eyes exhibiting the posterior segmental lesion which he called "Sudan blindness"; Hughes⁷ reported on one eye obtained at autopsy; Ridley,⁸ who was unlucky and obtained no eyes, did British ophthalmology a service, nevertheless, by reviewing the subject at a time when it was badly needed. This review has certain limitations based on the fact that it is a summarized version, part of a monograph on the entire subject of onchocerciasis. In the circumstances it would seem we were most fortunate to obtain the amount of material we did, for unlike most other workers no eye was bought, or obtained at autopsy; each was excised surgically, after selection, with full permission of the patient.

What, briefly, has emerged from this thesis?

All the evidence suggests that the dead bodies of *O. volvulus* microfilariae act as chemical poisons. Animal parasites are frequently living irritants, acting by virtue of toxins which they excrete, or by the mechanical irritation they excite. The adult *O. vol-*

volvulus may come into the former category as far as the degenerative lesion is concerned, but in all the other ocular manifestations it is almost certainly not involved. It is well adapted. The microfilariae are also well adapted during their lifetime. After they die, nevertheless, the products of their dissolution cause a violent but brief local reaction; the subsequent dilution and dispersal of the toxic products by the tissue fluid leads to a comparatively mild chronic phase. As the process of tolerance sets in, subsequent microfilarial deaths lead to less and less severe acute attacks, but prolong the duration of the irritation. For the greater part in the course of this disease, therefore, the toxins will act as stimulants to growth, different cells being activated to varying extents—rather than necrotizers. Thus initially we have a destructive lesion which is followed by insidious changes furthering those processes which lead to blindness unless tolerance occurs first.

Helminthic parasites are usually engulfed when they die by macrophages. In onchocerciasis as far as the microfilariae are concerned these cells are conspicuous by their absence, and when a few do appear it is

only in the late stages after the parasite has been absorbed; it is the dead tissues they are probably scavenging, especially debris within the chambers of the eye. This makes the condition unique. It also means the parasite bodies must be quickly fragmented and absorbed, although the products of disintegration seem to linger on for a while.

The cells which are present during the acute phase are eosinophil leukocytes, which conforms with the general idea that they are attracted by the products of animal parasites. These cells appear in the affected tissues quickly and disappear just as quickly early in the disease, although naturally an eosinophilia of the usual order in parasite infestations can always be found even in chronic infections. The fact that plasma cells and lymphocytes appear in large numbers, following the acute reaction, strengthens the view that antibody formation occurs.

Boyd⁹ believes that both these cells are concerned with the development of a complete or partial immunity, which, in fact, my experiments demonstrate. That I was unable to demonstrate the transfer of antibodies in the guinea pig or rabbit does not weaken the absolute results achieved in the second group of animal experiments and in man (especially) where a noxious dose of dead microfilariae injected under the conjunctiva produced a violent local reaction in non-infected subjects; on the other hand, in subjects who appeared to be immune to infection—by reason of the fact that parasites were present in their eyes in great abundance in the absence of any ill-effect—similar injections led to no reaction whatever. This seems to me to be an original observation of the highest importance.

As has been stated, a great many of the catastrophes in ocular onchocerciasis result from the processes of stimulation, or repair. This particularly affects the fibrocytes, the vessels, and the pigment cells. It is the growth of these cells into the cornea which turns it permanently opaque. The posterior uvea and the optic nerve suffer in the same way as a result of the proliferation of glia

and fibrous tissue. On the other hand, the exudate which occurs in the acutely affected eye is, if anything, even more prone to lead to blindness as it becomes organized. In the case of the degenerative lesion, where one does not seem to be dealing with an exogenous infection, sclerosis of the choriocapillaris is probably the dominant factor, whatever its origin.

These studies suggest how the problem of ocular onchocerciasis should be tackled therapeutically. The quicker the acute attack is brought under control, the fewer the complications (Rodger¹⁰); the question of an acquired immunity on the other hand needs fuller investigation.

It is unlikely, where microfilariae are found in the conjunctival biopsies and seen in the cornea and anterior chamber with the ocular biomicroscope in eyes that are perfectly quiet and reveal no signs of a previous attack, that none of the parasites (as many as 50 have been counted in such eyes) has died at the time of examination. It is even less likely that the invasion is a recent one. I have seen too many cases for this to be tenable.

The only explanation is that these eyes have acquired tolerance. But the idea of complete or partial immunity (tolerance) gains credence beyond these arguments when we consider the fact that very few at all of those who *have* ocular lesions go blind.

In short, the circle of reasoning always returns to the question of antibodies. As the latter consist largely of gamma globulins, their formation must depend upon the general protein reserve of the body. This is universally low, although to varying degrees, in onchocerciasis areas. But who is to say what the threshold values may be of the processes which determine the degree of immunity? There are too many imponderables here to make it a fruitful line of conjecture at the moment, not until my experimental conclusions have been confirmed by somebody else at any rate.

The greatest controversy at present revolves around the pathogenesis of the pos-

terior segmental lesion. The view expressed here, that there are two conditions, is clinically sound, and the evidence is incontrovertible that while one is caused by the death of microfilariae in the uvea, the other is not; it is only the pathogenesis of the latter lesion which remains in doubt.

The possibility that it is caused by a toxin secreted by the adult worms combined with a vitamin-A deficiency was based on evidence built up carefully from a number of findings, statistical, epidemiologic, physical, nutritional and pathologic; but it is still somewhat equivocal; nor, I admit, are the therapeutic trials very convincing.

It may be that it is the *death* of the adult filariae which releases (as a product of disintegration) a toxin poisoning the choroid and retina, the only difference between this conjecture and what we know happens in the case of the microfilariae being that the adults die outside the eyeball. For an adequate titer of toxin to arise this way one supposes several adult worms would have to die about the same time; from what we know of the natural history of onchocerciasis such

a theory fits in well with the age of onset of the posterior degenerative lesion which coincides in point of time with the expected deaths of the first adults originally placed in the body about the age of five years. Such then are the facts and figments.

In conclusion, it must be said that it is hoped this thesis may make onchocerciasis more credible to those who have not worked in endemic areas and are (not unnaturally) usually unconvinced at the enormity of the problem; it is also hoped that these studies may help to advance our knowledge to a stage where the ocular complications can be prevented, and a large underprivileged proportion of mankind given release from what can be called—without any suspicion of melodrama—a living death. A blind man in Africa is comparable to a mentally defective child in an impoverished family in the west; and there is no welfare state to take care of him.

ACKNOWLEDGMENT

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MALIGNANT MELANOMA OF THE UVEA*

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Malignant melanoma of the uvea is a relatively rare but very important condition with which the ophthalmologist must deal. The intent of this paper is to review some of the literature, pointing out the salient features of the disease, and then to report four cases illustrating some of these points.

Duke-Elder states that the disease occurs in from two to six times in each 10,000 eye patients seen. Based on the records of Moorfields Hospital from 1871 to 1925, this incidence remained rather constant during that period.¹

Various studies have shown a slightly higher occurrence in one sex but no statistically significant difference has been suggested in any large series, and some studies have shown more in males and others more in females.

The average age incidence is about 50 years; 45 percent of cases occur in the fifth

and sixth decades of life. Patients under 30 and above 80 years of age are rare.¹

Malignant melanoma is rare in the Negro race. In 1,600 cases reported by the Armed Forces Institute of Pathology in 1942 only eight occurred in Negroes.

Bilateral cases of malignant melanoma are very rare. Shine² reported the first pathologically proved case occurring in both eyes in 1930. The second eye showed the tumor three years after the first. The iris of one eye and the choroid of the other was involved. He also collected seven other cases in the literature, though these had not been proved pathologically. Cordes and Cook³ reported a case in 1948 with a malignant melanoma involving the choroid of one eye and the iris of the other. Reese² reported a proved case of malignant melanoma of the choroid of both eyes, the tumor becoming manifest in the second eye eight years after the first.

Heredity is seldom a factor in the occurrence of these tumors. Occasionally a pedi-

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gree will show a definite family tendency. Duke-Elder¹ cites one family, first reported by Nelleship, in which seven individuals showed malignant melanoma of the uvea in four generations.

ORIGIN

For many years these tumors were considered to be of mesodermal origin and were called sarcomas. Theobald,⁵ in 1937, presented evidence that the tumors arose from the Schwann cell. Only a few years before this report was published, several workers had presented evidence that melanomas of the skin were of neurogenic origin. The nevus cell is a modified Schwann cell. The occurrence of true nevi in the uvea was shown by Wilder⁶ in 1946. Reese formerly felt that the more malignant melanomas containing epithelioid cells arose from stromal melanoblasts. However, in a more recent study of tissue cultures of uveal melanomas, he concludes that they all arise from Schwann cells, and that the fascicular cells are better differentiated because they are slower growing.⁷

LOCATION

The majority of the malignant melanomas occur in the choroid. Reese² reports that, in 271 eyes enucleated for malignant melanoma at the Institute of Ophthalmology (New York) since 1933, there were 224 of the choroid, 24 of the ciliary body, and 23 of the iris. Of the 224 occurring in the choroid, 205 were localized, 18 extended into the ciliary body, and one into the ciliary body and iris. Of the 24 occurring in the ciliary body 15 were localized and nine extended into the iris. Of the 23 occurring in the iris 20 were localized and three extended into the ciliary body. These numbers are in close agreement, being within two percentage points, on each count, with the statistics originally reported by Fuchs in 1882¹ in which he found 85 percent in the choroid, nine percent in the ciliary body, and six percent in the iris. Most of the choroidal lesions occur on the temporal side posteriorly.

HISTOLOGY

Many cell types are seen, frequently in the same tumor. In spindle cells the nucleus is long and oval and the ends of the cells terminate in long fibers. Callender⁸ divided these into subtypes A and B. The spindle A has a delicate reticulum and poorly defined nucleolus. Spindle B has a coarser, deeper staining nuclear network and a dense round central nucleolus. These cells are arranged in closely packed bundles running parallel or in whorls, or they may be quite irregular. Fascicular cells are elongated oval or spindle-shaped and are arranged in columns, or fasciculi, around a central lymphatic or capillary. Epithelioid cells are larger and may be rounded or polygonal in shape, with an oval nucleus. They occur in a well-differentiated reticular stroma. Callender classified these tumors according to cell type as: (1) spindle A and B, (2) fascicular, (3) epithelioid, (4) mixed. The prognosis becomes increasingly worse with each type in the order listed.

Existing benign melanomas may become malignant. Reese² reports one case involving the iris and another involving the ciliary body. Other authors have reported cases in which a presumably benign lesion was observed for a number of years and then began growing. After enucleation, microscopic sections proved the lesion to be malignant. Asbury and Vail⁹ reported such a case that was kept under observation for three years before the tumor appeared to be growing. Albers¹⁰ observed a case for eight years before the lesion appeared to be growing actively and the eye was enucleated. Reese states that there is histologic, as well as clinical, evidence for this. He states that around the base of a malignant melanoma of the uvea there is a flatter zone of tumor tissue extending into the adjacent uvea which is usually more pigmented and composed of more mature cells. He further states that in microscopic sections very small malignant melanomas are seen to arise in the outer layers of the choroid, or in the suprachor-

roidea, and that this is the location of benign melanomas.

Benign melanomas may spontaneously become malignant or this change may be precipitated by long-standing irritation or inflammation. Thus, the incidence of malignant melanoma in pthysical eyes is greater than in eyes without inflammation. All pthysical eyes showing malignant melanomas are not of this category for, indeed, the process may work in reverse; that is, a malignant melanoma may show necrotic areas which are quite toxic and thus initiate the inflammatory process from which the eye may eventually become pthysical. Duke-Elder¹ quotes from an original German article by Leber and Krahnstover (1898) in which were collected 34 cases of malignant melanomas the authors felt were secondary to a long-standing inflammatory process; in 22 cases they felt the pthysical eyes were caused by toxicity of necrotic malignant melanoma. In any event all pthysical eyes should be viewed with the suspicion that they may harbor a malignant melanoma. Reese² states "the occurrence, therefore, of malignant melanoma in eyes which have been blind for a long time is encountered sufficiently often to be in itself a reason for enucleating these useless and disfiguring eyes."

COURSE

The course of a malignant melanoma is quite varied so that it is unwise to expect a certain chain of events. Thus, the classical description of Knapp that there are four stages—(1) symptomless, (2) glaucoma, (3) extraocular extension, and (4) metastasis—may apply to many tumors but by no means all. Metastasis may occur at any stage and may be widespread before any trouble in the eye is even suspected.

As has been mentioned, growth begins in the outer layers of the choroid or even in the suprachoroidea. In the majority of cases, growth progresses as a circumscribed tumor but in some it may be diffuse.

The circumscribed tumor is at first flat-

tened somewhat by the resistance of the sclera on one side and Bruch's membrane on the other. Later it breaks through Bruch's membrane and grows in a globular fashion into the subretinal space. The resistance of Bruch's membrane keeps the tumor constricted more in this region so that a mushroom shape is usually assumed. At this stage the retina usually becomes detached. It rests on the tumor and the surrounding retina is separated by exudate.

This richly albuminous exudate is formed partly by venous obstruction and partly by irritative or toxic reaction from the tumor.¹ If the tumor is in the superior portion of the eye, this fluid may gravitate inferiorly, forming a detachment that is entirely separated from the tumor itself. Iridocyclitis and glaucoma, or both, may supervene at any time. More rarely a definite hypotension may exist. The course of growth may be modified if the tumor gains early access through the sclera to a neural or vascular channel. In such event, the tumor may invade or penetrate the sclera along the channel without appreciably elevating the retina.¹¹

Diffuse malignant melanomas of the choroid spread through the uvea without forming a circumscribed tumor. They are usually slower growing and may not affect vision or give other objective signs for a long time. Since the sclera may be diffusely infiltrated, extraocular extensions may be more frequent. Metastases may occur before ocular signs are evident. Toxic effects are not usually present because necrotic areas do not occur as in the circumscribed growth. Duke-Elder states that these neoplasms are relatively avascular and therefore more dependent on preformed vessels for their growth as well as early metastasis.

Juxtapapillary tumors also take a different course. Beginning in the choroid near the disc the tumor grows around the termination of Bruch's membrane and spreads over the disc, appearing clinically to arise from the disc itself. Many such cases have been re-

ported in the literature and some authors have reported malignant melanomas of the optic disc. De Veer¹² reported a juxtapapillary tumor that clinically appeared to arise from the disc. He cites reported cases of malignant melanoma being primary in the disc and challenges all of these reports, stating that the pathologic evidence presented is inadequate and that he believes all of these reported cases were actually juxtapapillary in origin.

As noted earlier, malignant melanomas of the ciliary body represent only nine to ten percent of those involving the uvea. The course of growth is similar to that in the choroid. If it begins in the posterior part of the ciliary body, it forms a globular mass into the vitreous and forward into the posterior chamber. If it begins anteriorly, it invades the posterior chamber early and pushes the iris forward, then invades it and the angle of the anterior chamber. Duke-Elder states that extraocular extension along the perforating scleral canals is usually early in such cases.¹ There is a tendency for the tumor to form a ring growth in the ciliary body, spreading around the globe within the ciliary body. Reese² states that there are two reasons for this: (a) the tumor extends around the major arterial circle because of good blood supply and because the potential perivascular space offers little resistance, and (b) the ciliary body acts as a confined space due to tissue cleavages. Desquamated tumor cells may be carried by the aqueous to other sites to produce implantation growths in the trabeculae, on the iris, or in the angle.

Malignant melanomas of the iris are still more rare. Many authors have reported benign melanomas that underwent malignant changes while under observation. Coats¹³ (1902) reported 26 cases of benign melanomas of the iris, and seven of these became malignant while under observation. Duke-Elder¹ states that this is probably the usual origin of malignant melanoma of the iris. The malignant tumor may be a localized mass or a diffuse growth throughout the iris

stroma. The cells may desquamate, be carried by the aqueous, and form implantation growths, as in the case of malignant melanomas of the ciliary body. Ring melanomas may be formed. The average age of the patient with iris malignant melanoma is younger than those with the tumor in the ciliary body or choroid. In Reese's series the average age was 46 years. This is probably partly due to the fact that, as a group, these patients are diagnosed earlier than those with tumors occurring in the ciliary body or choroid. Cytologically more iris tumors contain nevus cells and some are entirely composed of nevus cells. Glaucoma, which may develop rather early, is present in a larger percentage of melanomas of the iris, due to obliteration of the angle.

DIAGNOSIS

As in any other malignancy early diagnosis is of paramount importance if treatment is to be successful. Terry and Johns¹⁴ reported in their first series of 94 malignant melanomas of the uvea that 44.6 percent were unsuspected clinically.

Objectively the ophthalmologist may visualize a pigmented lesion of the choroid. The size and amount of elevation may be helpful in deciding whether or not it is malignant. If it can be determined that there is a fairly large globular pigmented solid growth present, little problem in clinical diagnosis exists. Many tumors will not present this typical appearance.

Terry and Johns¹⁴ reported retinal detachment to be present in 85 of 94 melanomas of the choroid in their series. They stated that the retina over the tumor was usually smooth and free of undulations.

Pigment deposits may be present and newly formed blood vessels may be seen. The area of detachment is usually rather sharply defined. An accompanying serous detachment may make the margins less sharply defined but a difference can usually be seen in the appearance of the elevated retina with the solid tumor behind it and the

serous portion. There is less scattering of the ophthalmoscope light beam on the area of retina overlying the tumor and it has a thicker and whiter look, in addition to being free of undulations that may be present in the area of serous detachment. The absence of holes in the retina is also suggestive. Most spontaneous detachments begin peripherally, though many of the tumors begin more posteriorly and normal retina may be seen peripheral to them. While these signs in a retinal detachment are suggestive, their absence does not rule out the possibility of a malignant melanoma.

Rones and Linger¹⁸ studied slides of 117 malignant melanomas occurring in the posterior pole with no anterior pathology to impede ophthalmoscopic study. Their primary purpose was to try to determine any factors that might lead to an earlier and more accurate diagnosis clinically. They divided these cases into three groups. In Group I there was no bulging of the lamina vitrea, in Group II there was bulging, and in Group III the lamina vitrea had been broken through by the tumor.

Group I was composed of 18 cases in which there was no bulging of the lamina vitrea. Clinically these appeared as gray lesions with slight retinal elevation; five appeared as slate-colored retinal detachments. The commonest symptom was blurring of vision. Pathologically, they found that, even in these early tumors, there was cystoid degeneration of the overlying retina in 10 of the 18 tumors and in these 10 there were adhesions of varying degree between tumor and retina. In the remaining eight cases the tumor and retina were separated by serous exudate. They found pigmentation to be of no significance in these cases. Although the authors do not comment on field changes it would seem that measurable field loss should be present in the area of cystoid degeneration and in those cases with serous separation.

Their Group II was comprised of 48 cases in which the lamina vitrea was bulging, but

not broken through. Subretinal serous exudation was present in all but two of these cases but the amount of exudation bore no relationship to the size of the tumor. There was marked hyperplasia of the retinal pigment epithelium in 31 cases; 22 cases showed definite cystoid degenerative changes. Gliosis of the overlying retina occurred in 18 cases; in six of these it was associated with cystoid degenerative changes.

Group III was composed of 51 cases in which the tumor had broken through the lamina vitrea. These were selected cases that were felt still to present a diagnostic problem ophthalmoscopically in that the anterior segment was uninvolved. In nine of these the overlying retina showed gliosis or cystoid degeneration. In 26 the overlying retina was thinned and atrophic as a result of pressure from the tumor, and in 16 cases the tumor had completely broken through the retina. The authors felt that in these posterior lesions the primary clinical evidence for diagnosis was loss of vision and interpretation of the retinal detachment, differentiating it from other causes. They felt that pigment disturbance was of no diagnostic value.

Reese² does not agree with the idea that pigment disturbance is of no value. He states that, when the retina adheres to the surface of the tumor and contains pigmentary changes secondary to proliferation of the pigment epithelium, the detachment's appearance is that of an old chorioretinitis. In addition to these pigmentary changes drusen sometimes appear around the base of the lesion.

Subjective manifestations will depend on the site of the tumor to some extent. In the posterior pole increasing hyperopia may be the first finding, later to give way to blurred vision which is not correctible with lenses. If the tumor lies more peripheral, a large field defect may be present before the patient notices it. Hemorrhage into the vitreous may occur, with resulting loss of vision which is noticed by the patient. Uveitis may occur and cause the patient to seek help. As

a very rare occurrence a severe panophthalmitis associated with exophthalmos resulting from tumor necrosis may develop.²

When it is difficult to determine the nature of a detachment, bedrest with binocular bandage may be helpful. If the retina flattens down entirely, or lies in folds, it is probably only a serous detachment. On the other hand if a tumor is present the retina may remain globular, or the serous element subside enough to allow detection of the underlying mass.

The slitlamp may be of value in helping to differentiate a serous from a solid detachment. The serous detachment shows a translucency caused by the light's penetration of the subretinal fluid. When a solid tumor is lying immediately under the retina, the light is obstructed by the tumor and the translucent appearance is absent.¹⁶

Transillumination is a diagnostic aid that may be useful. However, in my experience the results are often difficult to interpret and may be misleading. Unless the growth is large and the point source of light small and of low intensity the lesion may be missed. Blood interferes with transillumination so that subchoroidal hemorrhage may be mistaken for a malignant melanoma. Transillumination is usually carried out by placing a small source of light external to the sclera and observing through a dilated pupil in a darkened room for any interference with the transmission of the light. The transillumination of Lancaster is very satisfactory.

In more posterior lesions an incision must be made in conjunctiva and bulbar fascia to introduce the instrument posteriorly. A variation of this is the method of Lindahl in which the fundus is observed with an ophthalmoscope, without its light being turned on, while a transillumination light is moved external to the sclera. Another variation for anterior lesions is to place a brighter source of light over the sclera opposite the lesion, observing to see whether or not there is any interference with transmission of light at the site of the lesion.

In his book, *Tumors of the Eye* (1951), Reese felt that transillumination was a useful adjunct to diagnosis of malignant melanoma of the eye. Since then he has modified his views and stated that he depends on it very little.¹⁷ He described a technique of "retroillumination" with the ophthalmoscope and believes this to be a useful adjunct when one has become familiar with the technique. This is carried out by using a direct ophthalmoscope. The light is directed on the lesion and moved over it and the surrounding retina. If a malignant melanoma is present, there is less scattering of the edges of the ophthalmoscope light because it is absorbed more completely by the tumor.¹⁷

Study of the visual field may be an aid in diagnosis. Malignant melanoma usually gives a dense scotoma. If there is a surrounding area of retinal detachment, this will also affect the field, but the loss here may be present only for smaller isopters, with a complete loss in the area occupied by the tumor.

The question of doing some type of biopsy has been discussed by many investigators. Needle biopsy, aspiration of subretinal fluid, and incision of sclera and biopsy with forceps have been reported on and discussed.

Diagnosis from subretinal fluid studies have not proved feasible from the standpoint of accuracy of diagnosis. Reese² states that he believes it to be impossible to be certain whether cells present are those of malignant melanoma or macrophages containing pigment. Christensen and Rowen¹⁸ undertook a rather extensive study of the cells in subretinal fluid. They too experienced difficulty in differentiating between malignant cells and macrophages, though they felt that this could sometimes be done. In 83 eyes that had been enucleated for malignant melanoma, they demonstrated tumor cells in the subretinal fluid of 45. Four eyes were examined prior to enucleation and tumor cells identified in three of these. Pathologic study of the eyes proved all four to have malignant melanoma. In three of these the tumor was ex-

tending through the diathermy punctures made at the operation to obtain the subretinal fluid; in one of these this occurred in 13 days. They concluded that, because of technical difficulties and the obvious danger of extraocular extension, this procedure should not be done.

Kauffman¹⁹ reported a case in which he did a needle biopsy of the tumor and made diagnosis of malignant melanoma. The eye was enucleated and examination proved the diagnosis correct. The patient died nine months later of a cerebral vascular accident without evidence of metastasis. At the same time this report was given, Zentmayer¹⁰ reported a similar aspiration biopsy with orbital recurrence of the tumor in a few months following enucleation.

Another study that may be an aid to diagnosis is the injection of radioactive isotopes with study of the uptake by the suspected lesion. Radioactive phosphorus is used instead of other isotopes because it emits beta radiation. Thus the penetration is shallow and there is not any effect from remote tissues. A suspected lesion in the anterior portion of the eye can be studied without interference with the normal uptake by the choroid. In a study by Terner, Leopold, and Eisenberg²⁰ the highest normal eye had a 28-percent uptake count. They consider an uptake of 30-percent or more as significant; this has been generally accepted by other writers. They feel that one count is not significant unless it remains up or increases, and do not make a positive diagnosis on a 30-percent count unless the count done 24 hours later is higher. Vascular tumors will show an increased uptake but this will fall on the 24-hour count, whereas malignant tissue will show an increase.

The technique of doing the counts is quite important and the application of the counter tip must be made very carefully and control areas on the other eye studied. Shapiro²¹ reports on 80 countings. Twenty-four of these were followed pathologically. Of these 24 there were three false negatives. He stresses the importance of individualizing the count-

ing and control areas in each patient, and of doing several counts so that an unquestioned trend may be noted. He relies chiefly on the 48-hour count.

Griffey, Whalen, and Allen²² reported on a smaller series of 25 patients. Six of these showed an uptake of more than 30-percent. Two of the six refused surgery; one of these died two months later of metastasis, the fate of the other is unknown. Four of the six had enucleations and three of these four had malignant melanoma and the other had a hemangioma. On this false positive no 24-hour count had been done. In two of the 24 patients who were not considered to have a significant uptake of P³², the eyes were enucleated and proved to have malignant melanoma.

Thus we see that, while this test may be a valuable adjunct to diagnosis, it is subject to error in giving both false negatives and false positives. In cases in which the diagnosis is reasonably certain from clinical evidence P³² studies should probably not be done because the test itself is not without some risk. In studying posterior lesions an incision has to be made through conjunctiva and bulbar fascia of both the affected and the normal eye and this incision has to be reopened at least once. However, it would seem that in doubtful cases these studies would be worthwhile and much safer than any type of biopsy.

DIFFERENTIAL DIAGNOSIS

In deciding whether or not a lesion of the choroid is a malignant melanoma the following conditions should be considered:

Serous detachment of the retina. This has already been discussed in detail. In a serous detachment the retina appears more translucent. It may be seen to move in a tremulous manner when the eye is rotated. Retinal folds may be present. The presence of a retinal hole speaks strongly for a serous detachment but failure to find one does not rule it out. Transillumination is good unless subretinal hemorrhage is present.

Intraocular hemorrhage. This is perhaps

the most difficult thing to differentiate. Choroidal hemorrhage may cause retinal elevation, simulate the appearance of a melanoma, and transilluminate poorly. Hemorrhage into the vitreous may obscure a clear view to the extent that the fundus cannot be carefully studied at all. If the hemorrhage is due to diabetes, hypertension, arteriosclerosis, or blood dyscrasia these changes can probably be seen in the fellow eye. It must be borne in mind that a malignant melanoma undergoing necrotic changes can cause hemorrhage.

In Kuhnt-Junius disease, or disciform degeneration of the macula, the lesion is usually elevated and of dark color and may closely resemble a malignant melanoma in this region. Important points are the presence of exudates or hemorrhages around the lesion and a similar process present or beginning in the fellow eye.

Detachment of the choroid. This usually follows soon after surgery and these cases should not be easily confused with malignant melanoma. However, choroidal detachment may follow injury or inflammation of the choroid or sclera, or the onset may be delayed following surgery. In addition to the importance of the history, there is no interference with transillumination.

The lesions produced by tuberculosis, syphilis, or sarcoid may resemble a tumor. General examination by an internist should help to establish the presence of the disease. Inflammatory signs may be present in the eye, though this is not pathognomonic because toxic reaction from the melanoma may cause a similar picture.

Hemangioma of the choroid may closely resemble a melanoma. Transillumination is of no help. In a recently reported series on the use of P^{32} , one eye with a positive uptake was removed and contained hemangioma. The presence of other hemangiomas in the eye or about the face would be strongly suggestive.

Metastatic carcinoma may resemble malignant melanoma but is usually lighter in color. Diagnosis of the primary site would be pre-

sumptive of this diagnosis in the eye, though the eye lesion may manifest itself before the primary site is known.²

Cyst of the retina. A large solitary cyst may occur with hemorrhage and resemble a malignant melanoma.

In the differential diagnosis of those lesions involving the ciliary body the following must be considered:

Intraepithelial cysts of the ciliary body.

Most of these are small but they may become large enough to push the iris forward to obliterate part of the angle, or forward to the cornea. When the cyst extends along the posterior surface of the iris it may resemble a melanoma. It is dark in color and the pigment epithelium comprising the cyst wall interferes some with transillumination. If the cyst arises from the corona ciliaris it transilluminates light. Another method of study is to observe the posterior chamber gonioscopically with dilated pupil; with this direct observation it may be easy to tell that the lesion is a cyst.

Malignant epithelioma may arise from the ciliary epithelium and be difficult to differentiate. Since treatment would be the same for either case, the clinical differentiation makes little difference.

Granulomatous lesions may occur in the ciliary body. Diagnosis of the systemic disease would be of help in making the diagnosis.

Leiomyoma and diktyoma are rare lesions that may occur in the ciliary body and resemble malignant melanoma.

In the differential diagnosis of iris lesions the conditions to be considered are much the same as those of the ciliary body. Iris cysts are the most common lesion. These may be implantation cysts of epithelium that has been implanted in the iris by perforating wounds. Intraepithelial cysts may be formed by the separation of pigment epithelium from underlying smooth muscle. This usually occurs in the pupillary area. Such a cyst may also occur at the base of the iris or in the ciliary body, pushing the iris forward as previously described. Leiomyoma may oc-

cur in the iris. It is poorly demarcated and contains little or no pigment and does not show implantation growths. Metastatic lesions, primary carcinoma, granuloma, lymphosarcoma, and encysted foreign bodies are other conditions to be considered.

TREATMENT

Once the diagnosis of malignant melanoma is established with reasonable certainty the treatment is usually enucleation. Enucleation should be done in all cases of malignant melanoma of the choroid and ciliary body unless it is felt that extraocular extension has occurred, in which case the orbit should be exenterated. In doing the enucleation, care should be taken not to dissect into any encapsulated extraocular extension. A long section of optic nerve should be obtained routinely, though it is rare for a melanoma to spread by this route. Examination of the globe should be made carefully and if unencapsulated extraocular extension is found, or if an encapsulated extension has been dissected into, exenteration of the orbit should be done.² Before doing an enucleation it is well to check the liver for enlargement and have a chest X-ray film to determine whether or not metastasis already exists. If there is definite evidence of metastasis, there is little point in removing the eye unless it is painful.

Circumscribed tumors of the iris may be removed by iridectomy rather than by enucleation. This should be done only when the lesion is well circumscribed and gonioscopic examination shows the angle to be clear.

Treatment other than surgical removal should be strictly a second choice. Several authors have reported on treatment with surface diathermy in the case of malignant melanoma of the patient's only eye. The very early results in some of these cases seem promising, but the literature does not contain adequate follow-up to draw any valid conclusions.

Radiation has been used. Duke-Elder states that it is of no value as a primary treatment but is worthwhile postoperatively.¹

Reese sharply disagrees, and the following is a direct quotation from him: "Irradiation in any form is without benefit in arresting the primary growth, in controlling residual or recurrent tumor in the orbit, in preventing metastasis, and in prolonging life. Moreover, it is of no value as a postoperative prophylactic measure. Not only is the tumor tissue entirely radioresistant but also there is some evidence to indicate that the tumor growth may be stimulated by irradiation."²

PROGNOSIS

The most complete statistical study on follow-up was that reported by Callender, Wilder, and Ash²³ in which they studied 1,600 cases on file in the Armed Forces Institute. In 500 of these there was at least a five-year follow-up. The mortality on these 500 cases after five years was 48 percent. A 10-year follow-up was obtained in 200 cases and the mortality rate increased to 66 percent.

Certain histologic characteristics are of definite prognostic significance. The authors studied these 500 cases from several standpoints and their results were: The different cell types comprising the tumor had a very different rate of metastasis. Least malignant was spindle A, the mortality rate being six percent in five years. These cases comprised a total of 35. Tables 1 and 2 were taken from their report.

The authors also studied the 500 eyes from the standpoint of pigment content, and reported their findings as in Table 3. Though there appears to be an increased mortality with increased pigment content, the authors did not feel that this one series justified definite conclusions in this respect.

TABLE 1
OUTCOME ACCORDING TO CELL TYPE

	Living	Dead	Total	% Fatal
Spindle A	33	2	35	6
Spindle B	88	29	117	25
Fascicular	8	5	13	38
Necrotic	23	22	45	49
Mixed	105	171	276	62
Epithelioid	4	10	14	71

TABLE 2

OUTCOME ACCORDING TO ARGYROPHIL-FIBER CONTENT

	Living	Dead	Total	% Fatal
Heavy	17	2	19	10
Marked	58	32	90	36
Medium	80	63	143	44
Light	101	122	223	55
Absent	5	20	25	80

The mortality according to cell type is in accord with that of neoplasms in general, in that the more anaplastic the cell the more malignant is the tumor. The spindle cell is the least anaplastic and the epithelioid the most. Reticulum is one of the intercellular elements that can be stained alone with the Wilder silver stain, thus the name argyrophil fiber. The more anaplastic epithelioid cell lays down the least reticulum and the slower-growing spindle cell the most, so that these tables run roughly parallel.

Another factor of significance in the mortality in cases of these tumors is the time elapsed between onset of the tumor and the enucleation. No such study is possible because in most cases the time of onset is not known. Unless the tumor occurs in the posterior pole, causing some blurring or distortion of vision, the patient may not suspect it for a long time. Terry and Johns¹⁴ reported in their first series that 44.6 percent were unsuspected clinically. Reese² reports figures of mortality originally reported by von Hippel and von Papolczy in which the mortality in cases of eyes enucleated in the first stage of the disease is 33 percent, in the second stage 45 percent, and in the third stage 90 percent. These figures do not show the time of onset but certainly support the idea that the earlier enucleation is done the better is the prognosis.

TABLE 3

OUTCOME ACCORDING TO PIGMENT CONTENT

	Living	Dead	Total	% Fatal
Light	93	48	141	34
Medium	114	121	235	51
Marked	50	61	111	55
Heavy	4	9	13	69

The host's resistance to malignancy is another unknown factor of which there is no measure. Thus in some individuals the malignant cell lies dormant for many years after the eye is enucleated before it metastasizes; in others the time is much shorter. Death from metastasis may occur as late as 20 or 25 years after the eye has been enucleated. It does not seem unreasonable to assume that the same thing occurs in the case of the primary growth; that is, that the same type tumor histologically may take longer to grow in one patient than in another.

Extraocular extension causes an increase in fatalities. In the Armed Forces Institute series, six percent had extraocular extension and the five-year fatality in this group was 67 percent, this being 19 percent greater than the average without extraocular extension. Duke-Elder¹ cites patients reported by Spicer (1912) and Denecke (1936) who were alive without evidence of metastasis 13 years after enucleation, though they had evident extraocular extension at the time.

Recurrence in the orbit carries a more serious prognosis. Reese² reports eight such cases in his personal experience. The mortality rate in these was 100 percent and the average time of death 15 months after the orbital recurrence.

Callender, Wilder, and Ash²³ reported three deaths in 32 malignant melanomas of the iris for a mortality rate of 9.4 percent. Three of the living patients had only an iridectomy. It was felt that earlier diagnosis was probably a large factor in the lower mortality from these tumors.

Chisholm²⁴ restudied Terry and Johns' series of 94 cases, first reported in 1935, from the standpoint of longer follow-up. He found that of those patients dying from spindle-A and spindle-B tumors the average time between enucleation and death was 10.5 years. The patients with fascicular, epithelioid, and mixed tumors died in 3.8 years.

Compared with malignant melanoma elsewhere in the body the prognosis is better in the eye. Pack and Scharnagel,²⁵ in reporting on 575 cases of nonocular malignant mela-

noma, showed a five-year cure of 21.4 percent. This varied according to location. Ten cases of anorectal lesions had no survivals. Oronasal had 9.1 percent five-year survival, trunk 13.7 percent, subungual 38.9 percent and palm 97.5 percent. The authors felt that two factors were responsible for this, early diagnosis in some sites and accessibility of wide excision. Seventy-three percent of this group were considered operable when first seen and immediate surgery cured 39.9 percent. Delay of more than one month in surgery gave 17 percent less cure.

As has been reported earlier in this paper, the cell type of the intraocular melanoma is of definite prognostic significance. It would seem that another factor of definite importance is the location of the tumor inside the eye. The density of the encasing sclera is a limiting factor in the tumor's growth as well as helping to insure its complete removal, except in a small number of cases in which extraocular extension has occurred. It would seem that this must play some part in the lowered mortality of intraocular malignant melanoma. In the group of nonocular malignant melanomas reported by Pack and Scharnagel,²³ there was a marked difference in mortality, ranging from 12.5 percent, fatalities from those lesions on the palm to 100 percent from those in the anorectal region. No mention is made of any difference in cell type. The authors felt the difference to be due to early detection and accessibility of wide excision. As previously stated it was felt that delay of more than one month in surgical removal increased mortality 17 percent.

In the eye most of the tumors probably go a good many months before detection, some of the slower-growing ones perhaps for years. Probably the time of removal from the eye is not so important to the prognosis as removal elsewhere in the body because the encasing sclera may limit its growth. The factor of "accessibility of wide excision" is greatly eliminated by the tumor usually being contained within the sclera.

It would seem then that both the cell type of the tumor and the structure of the eye itself, as compared to the body elsewhere, are factors that give a better prognosis to intraocular melanoma.

CASE REPORTS

CASE 1

Mrs. E. W. was 83 years of age when first seen on August 28, 1952. She complained of pain in the right eye and blindness for three months. Vision, O.D., was no light perception; O.S., 20/40. Intraocular pressure (Schiotz); O.D., 64; O.S., 17 mm. Hg. The right eye was injected and the cornea edematous. Enucleation was advised and refused. A retrobulbar injection of alcohol was done and this relieved the pain. On September 14, 1953, the eye was again painful and a dark elevated mass could be seen on the globe behind the limbus superiorly. It was felt that this might be a melanoma. Surgery was again refused. Another year passed and the globe eroded in this area with some drainage of dark material; a smear of this showed it to be a malignant melanoma. Her internist found no clinical evidence of metastasis at this time; X-ray studies were not done. The patient died in January, 1955, at the age of 86 years. Post-mortem studies were not done. Death was attributed to cardiac failure.

CASE 2

Mr. J. R. B., a 72-year-old man was seen on March 9, 1956, with complaint of loss of vision in the left eye. History revealed some light flashes in the lower field about five months previously, vision had been noticeably reduced for two months. Vision: O.D., 20/20; O.S., finger counting. A large dark mass was visible superiorly. Examination by an internist revealed an enlarged liver, chest X-ray films were negative. It was decided to have a liver biopsy and to proceed with enucleation at the same time if this was negative for melanoma. However, biopsy revealed extensive liver metastasis and the enucleation was not done. The patient died April 14, 1956. The eye was not obtained. The liver biopsy showed many epithelioid cells.

CASE 3

Mr. F. D., a 68-year-old man, was seen first March 26, 1954, because of some irritation and pain in his left eye. History was given of having surgery for glaucoma, O.S., in 1950 with some vision retained for six months. Then several intraocular hemorrhages had occurred. Schiotz tension: O.D., 15; O.S., 42 mm. Hg. There was some ciliary injection, O.S., and blood staining of the cornea. The right anterior chamber was of normal depth, fundus and field normal. Enucleation was done April 5, 1954. Microscopic sections showed a spindle-cell malignant melanoma in the anterior segment. The patient was last seen in January, 1957, without evidence of recurrence, metastasis, or glaucoma in the right eye.

CASE 4

Mr. O. L. This 50-year-old man was first seen July, 1953, with the complaint of blurred vision in his left eye. His glasses had been changed three months before and vision had been good at that time. Vision, O.S., 20/60, improved to 20/25 with the addition of a +1.25D. sph. There was a slightly elevated faint gray lesion seen in the macula about 0.5 disc diameter in size. The patient was told that it might be a hemorrhage and might be a tumor and to return in six weeks for follow-up. He did not keep this appointment and was next heard from a year later (December, 1956) through another ophthalmologist who had enucleated his eye two months earlier for malignant melanoma. He was apparently in good health.

COMMENT

Case 1 presents a unilateral glaucoma without evidence of glaucoma in the fellow eye. Melanoma was probably present at that time, though the fundus could not be visualized. The patient lived two and a half more years without evidence of metastasis, though the tumor eroded the ruptured globe.

Case 2 presents quite a contrast. First symptoms were five months prior to the pa-

tient being seen, and metastasis was already well established in the liver; the patient died a month later.

Case 3 presents another case of unilateral glaucoma without any evidence of glaucoma in the fellow eye. Again the fundus could not be visualized but enucleation revealed a malignant melanoma.

Case 4 represents a case in which the symptoms of blurred vision were noticeable very early because the tumor was in the posterior pole. Its growth was relatively slow.

Both Cases 3 and 4 present the problem of patients failing to return for adequate follow-up observation and eventually changing doctors, one patient leaving another doctor and coming to me, and another leaving me and going to another doctor. In each case, the second doctor was not consulted in order to obtain a second opinion but was seen only after considerable time had elapsed and symptoms had increased.

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NOTES, CASES, INSTRUMENTS

DIKTYOMA*

(EMBRYONAL MEDULLO-EPITHELIOMA)

REVIEW OF THE LITERATURE AND
REPORT OF A CASE

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AND

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The malignant tumors which originate in the ciliary portion of the retina (*pars ciliaris retinae*) are rare. There are two forms, the adult medullo-epithelioma which develops in adult people and the embryonal medullo-epithelioma, or diktyoma, which occurs in young individuals.

In addition, benign growths have been described arising in the ciliary epithelium, such as the benign epithelioma of Fuchs,¹¹ which is an epithelial hyperplasia appearing in senile eyes affected with chronic inflammation,³⁶ and the adenoma of the ciliary body^{20,38}, also quoted by Grinker.¹³

Fuchs¹¹ and Nordmann¹⁸ have extensively described these tumors. The former in 1908, described four cases of a tumor which he called "diktyoma" (from Greek, *diktyos* = net), due to the peculiar arrangement of cells forming netlike structures. Verhoeff³⁴ suggested, in 1904, the name of teratoneuroma because he found structures of nerve origin within the tumor.

Medullo-epithelioma is the best name to express the origin^{8,11,20} of this tumor. Few diktyoma cases have been published in the literature and according to Reese²⁰ there are less than 80. Some of the published cases are listed in Table 1.

Andersen in a review of the literature

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found 22 cases, among which seven were considered to be doubtful.¹

In addition, we know of three more cases, reported to the Ophthalmic Pathology Club in Washington, D.C., by Wadsworth, Christensen, and Rones,²² in 1951, 1955, and 1956 respectively. To these may still be added another recent case studied by Christensen⁵ in 1958.

Diktyoma is a tumor which arises from the undifferentiated neuroectoderm of the primary optic vesicle. Because of its slow growing and slightly invasive power, the correct diagnosis is usually not established until after the eyeball is enucleated and the microscopic study of the specimen is performed. Usually, the clinical diagnosis is retinoblastoma or pseudoglioma of the retina.³⁴

The purpose of this paper is to report a case of diktyoma (embryonal medullo-epithelioma) which showed a great invasive power.

REPORT OF CASE

J. P. A., a 13-year-old boy, at two years of age had whitish spots in his left eye with impairment of vision. When he was 11 years of age, the eye suffered traumatic rupture and subsequently was enucleated. Since that time a tumorlike tissue was noticed growing within the orbit. The tumor mass enlarged to 10 by 6.0 cm. during two years, and by that time the patient was admitted to the Service of Ophthalmology of the General Hospital in Mexico City. The intraorbital tumor was firm, warm, and adherent to deeper tissue.

Laboratory examinations and X-ray films of the thorax were negative. X-ray films of the skull showed persistence of the metopic suture with separation of the edges and deformity of the left orbit, all due to an oval tumorlike tissue, and invasion of the maxillary antrum and surrounding tissues.

Ten days after admission, on September 26, 1957, a biopsy of the tumor was taken and the microscopic study revealed that the tumor cells were arranged in several rows as is found in the embryonic retina when differentiation of nuclei in individual layers has not yet occurred. The cells borders were perceptible, the nuclei were elongated, rounded, and deeply basophilic. Tumor cells formed solid masses or were arranged in cords which surrounded a central blood vessel. The stroma was scanty (fig. 1). Occasionally the cells formed cavities, which were concave on one side and convex on the other side. The concave side which invaginates toward the

TABLE 1
SOME OF THE PUBLISHED CASES OF DIKTYOMA

Author	Year	Author	Year	Author	Year
Badal and Lagrange ³	1892	Cucchia ⁶	1928	Czukurász ⁷	1941
Emanuel ⁹	1900	Satanowsky ²⁰	1928	Imre ¹⁸	1941
Verhoeff ²⁴	1904	Böck ⁴	1929	Shepkalova ²⁰	1941
Kuthe and Ginsberg ¹⁷	1905	Van der Hoeve ²¹	1930	Rubino ²³	1941
Greeves ¹²	1911	Soudakoff ²⁹	1936	Rubino ²⁴	1942
Spicer and Greeves ²⁰	1914	Shepkalova ²⁷	1938	Asbury and Vail ²	1944
Velhagen, et al. ²⁸	1917	Satanowsky, et al.	1939	Andersen ¹	1948
Hine ¹⁴	1920	Klien ¹⁶	1939	Fralick and Wilder ¹⁰	1949
Redslob ¹⁹	1923			Reese ²¹	1957*

* This tumor did not originate in the ciliary portion of the retina but in the optic papilla.

cavity shows several layers of nuclei, while the convex side has only one or few cellular layers. This structure closely resembles the embryonal retina when formation of the secondary optic vesicle is taking place (figs. 2 and 3). In some areas tumor cells were arranged in a more dense pattern, giving rise to rosettelike structures. Within the stroma there was a mucoid substance similar to vitreous humor, which was positive for mucopolysaccharides.

Eighteen days after the biopsy was taken, Dr. R. Segovia excised the tumor and both eyelids and found the lower portion of the frontal bone and the roof of the orbit destroyed by invasive tumor (fig. 4). During the operation the meninges were accidentally sectioned.

The patient was sent to the Cancer Service of the General Hospital where Dr. Ernesto Fernández found him in poor condition, with a pulsating and painful tumor mass measuring three cm. in diameter and located in the roof of the orbit. The tumor extended over the superciliary arch and was covered with necrotic tissue. There was mydriasis in the right pupil, poor vision, nystagmus, vomiting, and dizziness. The cerebrospinal fluid was yellow-greenish with slightly increased density. On January 1,

1958, the patient appeared restless. Death occurred on the same day.

Autopsy was performed in the Pathology Unit of the General Hospital. It was found that the tumor was invading the roof of the orbit and the skin and bone of the left supraorbital region (figs. 5 and 6). The right eye was normal. The dura was adherent to the surface of the brain which was covered with a thick coat of yellow-greenish material. The brain weighed 1,600 gr. The meningeal inflammatory process was more marked on the left side where it covered the temporal and parietal lobes (fig. 7). On the temporal lobe a prominent area whose anteroposterior diameter measured five cm. was observed. Many sections taken through different levels of the brain showed the tumor extending to the upper portion of the temporal lobe and widely invading the frontal lobe. The ventricular system was filled with greenish, semifluid material (fig. 8). The frontal bone was partially destroyed by invasive tumor and a close relationship between the tumor within the frontal lobe and frontal bone was found. The spinal cord revealed an intense meningitis.

On microscopic examination the tumor proved to have the same histologic structure found in the

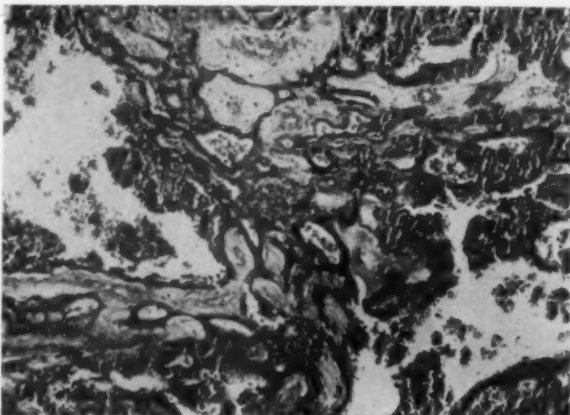


Fig. 1 (De Buen and González-Angulo). Low-power photomicrograph, showing the characteristic netlike arrangement of tumor cells. (Hematoxylin-eosin.)

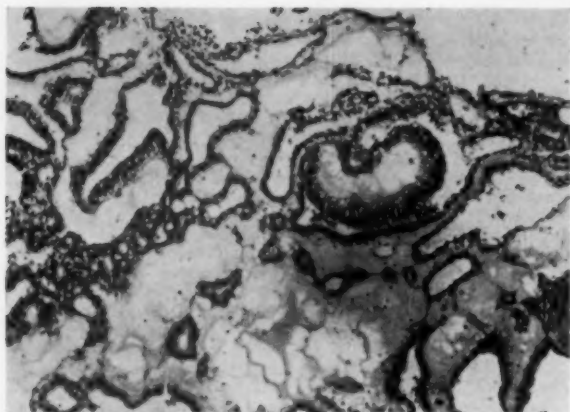


Fig. 2 (De Buen and González-Angulo). Another area of the tumor in which a structure closely resembling a secondary optic vesicle can be seen. Low-power magnification. (Hematoxylin-eosin.)

Fig. 3 (De Buen and González-Angulo). High-power view. Notice that the tissue in front of the cup has grown, suggesting an early development of the lens as one sees in the normal development of the eye by the so-called inductive differentiation. (Hematoxylin-eosin.)

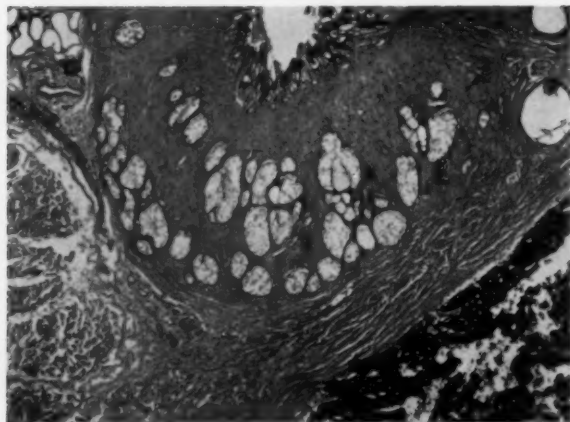
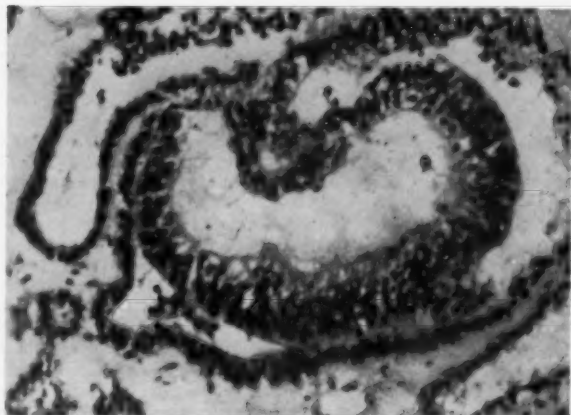


Fig. 4 (De Buen and González-Angulo). Low-power view of the tumor invading the upper eyelid. Meibomian glands, glands of Moll and striated muscle are shown. (Hematoxylin-eosin.)

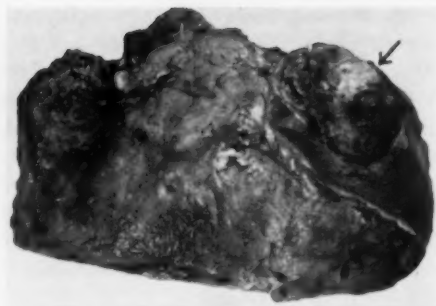


Fig. 5 (De Buen and González-Angulo). Photograph of the external surface of frontal and parietal bones showing the tumor mass (arrow) protruding through the orbit. A portion of the surrounding skin can still be seen.

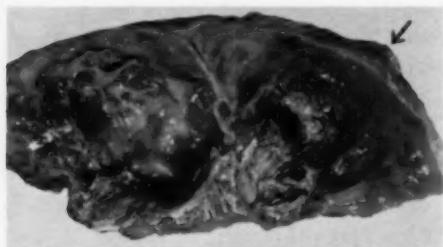


Fig. 6 (De Buen and González-Angulo). Internal view of the same portion of the skull showing the tumor on the roof of the orbit and extending outward (arrow).

previous biopsy and surgical specimen. The tumor was demonstrated microscopically in the same places where it was grossly found (figs. 9, 10 and 11).

There were no other demonstrable abnormalities in the body with the exception of an *ascaris lumbricoides* which was found in the terminal ileum.

DISCUSSION

During its development, the diktyoma reproduces the structure of embryonal retina. The epithelial cells which form the non-pigmented epithelial layer of ciliary body are derived from the retinal germinative cells. These did not differentiate into true retina but retained their epithelial properties.

Fig. 9 (De Buen and González-Angulo). Low-power view of tumor cells invading the brain. (Hematoxylin-eosin.)



Fig. 7 (De Buen and González-Angulo). Photograph showing the basal meningitis and tumor in the left frontal lobe.

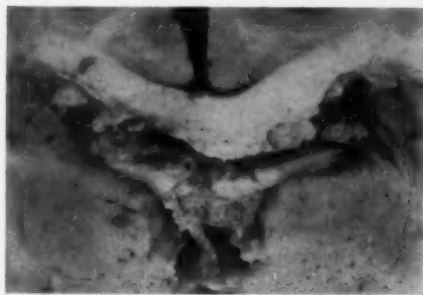
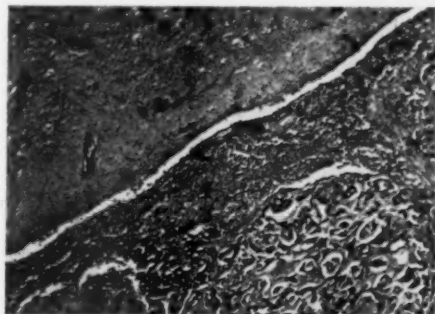


Fig. 8 (De Buen and González-Angulo). Photograph showing purulent material within the ventricular system.



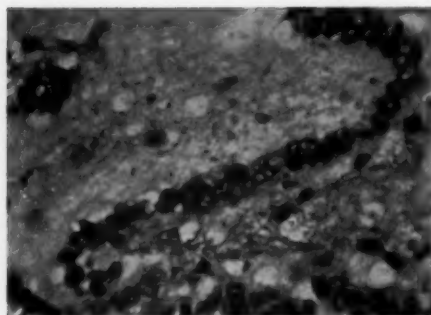


Fig. 10. (De Buen and González-Angulo). High-power view of tumor cells. (Hematoxylin-eosin.)

Diktyoma occurs in young people, the average age being five years,²⁰ although Böck⁴ reported a case of a 16-year-old girl; Soudakoff²⁹ published a case of a 28-year-old man, Rubino²⁸ another, in a 19-year-old man, and Hine¹⁴ a case of a 28-year-old man.

Diktyoma originates in the pars ciliaris retinae although theoretically the iris could also be the primary site.²⁰ Recently Reese²¹ reported a diktyoma arising in the optic papilla. Wolter³⁶ and Reese stated that diktyoma may arise in any portion of the retina.

The case herein reported, which has been mentioned by Lorenz E. Zimmerman in Lauren V. Ackerman's *Surgical Pathology* (St. Louis, Mosby, 1959, p. 1073) showed a great invasive power, with destruction of the frontal bone and invasion of the brain. There was extension by continuity from the orbital location into the brain, as has been found by other authors.^{20, 36} The tumor formed pseudorosettes in some areas, similar to those seen in retinoblastoma. In other places, the cells were arranged in one or several layers as in embryonal retinas. In none of the sections was it possible to identify cartilage as Böck,⁴ Shepkalova,^{27, 28} Klien,¹⁶ Fralick and Wilder¹⁰ were able to demonstrate. There were no cones and rods as has been reported,²⁰ or glial tissue as Verhoeff,³⁴ Böck⁴ and Velhagen have found. Fralick and Wilder designated "glioneuromatous diktyomas"¹⁰ those diktyomas with glial tissue.

The demonstration of primary optic vesicles in adult medullo-epithelioma has lead Wolter³⁶ to the conclusion that there is a possible relationship between this tumor and diktyoma as has been pointed out by Fuchs¹¹ and Andersen.¹

In the present case the exact site of origin of the tumor is unknown, although probably it was in the pars ciliaris retinae, taking into consideration the very high predominance of this site over the others.

This case is of great value because of the postmortem studies which revealed a lack of metastases, since the extension to the brain was exclusively due to direct continuity. This finding confirms what is generally accepted. Also the patient did not improve under X-ray therapy which is the same as reported previously by other authors.

The histologic morphology of the diktyoma is so typical that the diagnosis could be established even without having to study the primary tumor within the eye.

The exact diagnosis of diktyoma is strictly microscopic. However, it should be considered in the differential diagnosis of intraocular tumors, especially in youthful patients.

Another interesting fact is that it was possible to study the natural history of the tumor for a much longer period of time than usual. In general, the eye containing the diktyoma is enucleated, and when the microscopic diagnosis of diktyoma is established the tumor has already been totally excised.

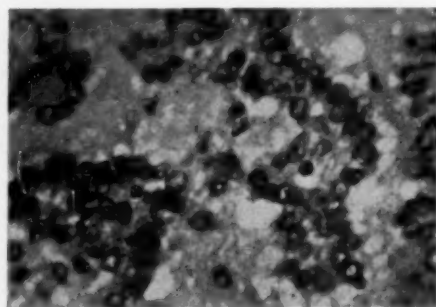


Fig. 11 (De Buen and González-Angulo). High-power magnification of another area of the tumor. (Hematoxylin-eosin.)

SUMMARY

A case of diktyoma (embryonal medullo-epithelioma) in a 13-year-old boy is reported. The tumor had probably grown since the patient was two years of age. The tumor invaded the left frontal bone and brain, and the patient died with a generalized cerebro-spinal meningitis.

A review of the literature with a more detailed study of some of the more interesting reported cases is presented. Some authors stated that the total number of published cases is less than 80. The average age of the patients is five years, although there

are cases reported in an older age group.

Diktyoma arises in the undifferentiated neuro-ectoderm of the primary optic vesicle. It grows slowly and usually shows a slight invasive power, growing within the eye first and extending into the orbit later. It does not metastasize. X-ray therapy does not seem to modify this tumor.

The microscopic picture of diktyoma is described and its relation with adult medullo-epithelioma is mentioned.

The diagnosis of diktyoma can only be made by microscopic study.

Adolfo Prieto 709-10 (12).

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UVEAL MALIGNANT MELANOMAS*

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AND

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During the last five years 14 eyes with malignant melanoma of the ciliary body and choroid have been diagnosed at the Marquette University Department of Ophthalmic Pathology. This represents about 10 percent of the eyes studied.

Malignant melanoma is the most common malignant intraocular tumor. It is almost always unilateral and the most usual site is the posterior choroid. Malignant melanomas of the choroid and ciliary body usually manifest themselves in adult life and are extremely rare in children. In the extensive statistical studies that have been conducted on the material in the Registry of Ophthalmic Pathology, the highest frequencies for this tumor are found in the fifth and sixth decades. The average age of patients with a malignant melanoma of the iris is from one to two decades younger than that of patients with a malignant melanoma elsewhere in the uvea. The racial incidence is striking, the tumor being extremely rare in Negroes. It occurs with equal frequency in males and females.

ETIOLOGY

There is some controversy as to the etiology of malignant melanoma but evidence suggests that the neoplasm originates either from the Schwann sheath of the ciliary nerves or the stromal melanoblasts of the

uvea. Normally the Schwann cell does not produce pigment but in pathologic states it becomes very versatile and may produce melanin. A tumor arising from this cell or the stromal melanoblast may be benign or malignant. A benign melanoma may be activated into a malignant growth by irritation from inflammation or perhaps trauma.

DIAGNOSIS

Ophthalmoscopy reveals a brownish to slate-gray colored lesion. Except when there is a retinal detachment, the tumor usually gives a solid globular appearance (fig. 1). There is a relative or absolute scotoma if the lesion is near the macular region. If the neoplasm is located away from the macula it does not manifest itself until an appreciable defect occurs in the visual field. Secondary glaucoma or an iridocyclitis frequently cause the presenting symptoms. A hemorrhage in the vitreous or anterior chamber with or without glaucoma may be the first manifestations. Tumor necrosis seems to be the most common cause of hemorrhage and inflammation. Under all conditions which interfere with direct observation of the lesion it is usually necessary in making the diagnosis to rely on history, transillumination and other aids, such as uptake of radioactive phosphorus. It is interesting to note that about 10 percent of eyes with malignant melanoma have opaque media. Biopsy for diagnosis of melanoma of the uveal tract has very few indications because of unreliability and possibility of disseminating the tumor.

Perimetry is very helpful in differentiating between a benign and malignant melanoma of the choroid. A change in the visual field is sufficient evidence to diagnose the lesion as malignant. A field defect from a malignant melanoma is larger than would be

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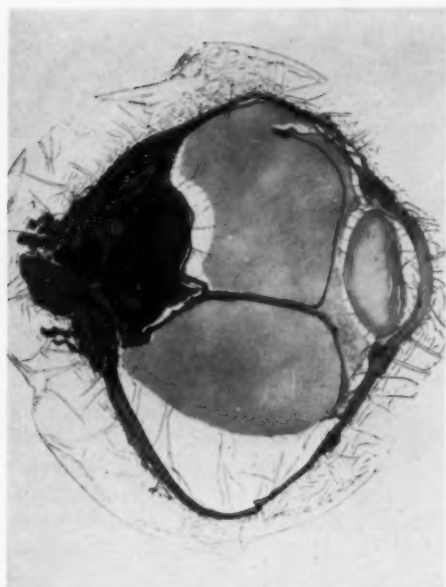


Fig. 1 (Holm and Kaufmann). Malignant melanoma of the choroid. Neoplasm not diagnosed preoperatively due to cataract. Note densely pigmented globular mass protruding toward the vitreous cavity and retinal detachment. ($\times 3.5$.)

expected. Benign choroidal melanomas result in no field defect. Subretinal fluid studies for tumor cells and melanin in retinal detachment when tumor is suspected are unreliable. If there is doubt as to the diagnosis, enucleation should be delayed until a series of fundus photographs and careful drawings can be compared over a period of time.

HISTOLOGY AND PROGNOSIS

Callender's histologic classification of intraocular malignant melanomas gives reliable information concerning prognosis. This classification is based on three cell types: spindle-A, spindle-B, and epithelioid. In addition, there is a variety of spindle-cell melanoma characterized by palisading of the nuclei of the tumor cells. This is called the fascicular type. Those tumors containing mixtures of spindle and epithelioid cells are classified as mixed. Some tumors are too necrotic to be classified otherwise. Of the

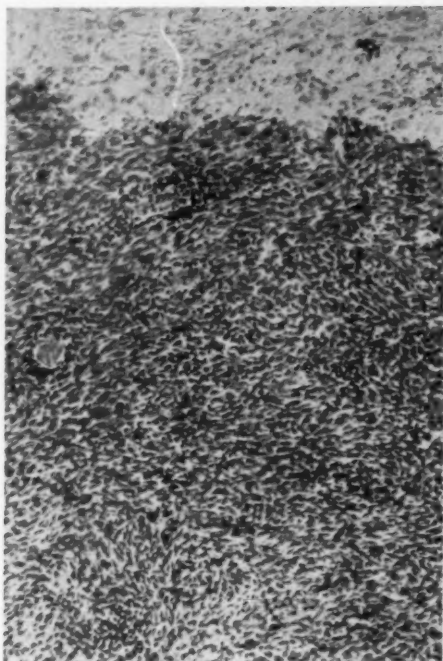


Fig. 2 (Holm and Kaufmann). The same case as Figure 1 showing spindle cell structure (subtype B) of the tumor ($\times 150$).

types enumerated the "mixed" is the most common, accounting for more than one-half

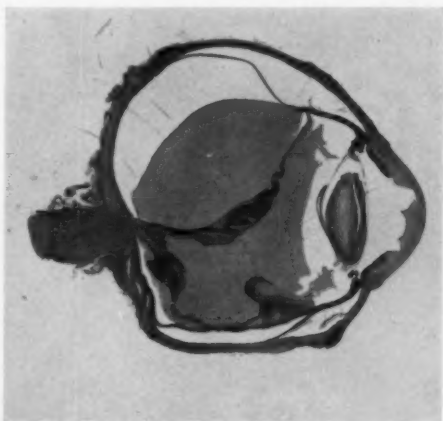


Fig. 3 (Holm and Kaufmann). Retinal detachment and chronic enophthalmos. Blind eye enucleated because of the possibility of a malignant melanoma ($\times 3.5$).



Fig. 4 (Holm and Kaufmann). Vitreous hemorrhage, blood staining of the cornea, glaucoma, cataracts and uveitis. Blind painful eye which did not transilluminate. Enucleated because of the possibility of a hidden malignant tumor ($\times 3.5$).

of all malignant melanomas of the ciliary body and choroid. The tumors composed of

the spindle cell (fig. 2) have the best and those in which the epithelioid cell dominates have the poorest prognosis. Malignant melanomas of the iris have comparatively low mortality. It is thought that a factor in the lower mortality of these tumors is their earlier detection. Another histologic factor of prognostic significance is the argyrophil fiber content of the tumor. In an analysis of 500 cases by Callender, Wilder, and Ash it was concluded that the heavier the argyrophil fiber content, the better the prognosis.

The mortality for a five-year period is about 50 percent and some 16 percent of the survivors die in the second five years after enucleation. In the succeeding five-year periods the deaths from generalized malignant melanoma continue but at a declining rate. Metastatic deaths have been reported as long as 35 years after enucleation. Metastases may appear in almost any organ of the body but their most common site is the liver. According to Callender and Wilder the highest death rate among cases observed occurs in patients in the eighth and ninth decades of life. Extraocular extension of the tumor is an indication of poor prognosis. Early diagnosis increases the patient's prognosis for



Fig. 5 (Holm and Kaufmann). Kuhnt-Junius disciform macular degeneration. The eye was enucleated following a clinical diagnosis of neoplasm. Elevated mass near macula involving the choroid and retina with scalloped areas of retinal pigment in the periphery ($\times 60$).

life. In a study of 210 melanomas of the choroid and ciliary body it was shown that the 105 patients with the larger tumors had a significantly poorer prognosis than the 105 patients with small tumors.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis of malignant melanomas of the choroid the following conditions must be considered: inflammation (granulomatous lesions), proliferative type of macular degeneration (Kuhnt-Junius), benign melanoma of the choroid, metastatic carcinoma, serous detachment of the retina, detachment of the choroid, hemorrhage in the choroid, subretinal space or vitreous, hemangioma of the choroid, Coats' disease, cyst of the retina, and several other less common conditions. In the literature there are many reports of eyes enucleated because of an erroneous diagnosis of malignant melanoma. In a large recent series of eyes enucleated with a clinical diagnosis of malignant melanoma, 12 percent were found to be non-malignant on histologic examination. According to statistics gathered at the Armed Forces Institute of Pathology, of 969 patients, 30 years or older, with eyes blind for more than six months' duration, that came to enucleation, four percent harbored malignant melanoma. Reese is of the opinion that when the eye concerned is obviously irrevocably blind, enucleation is indicated on the ground that it would be too risky to leave the eye.

TREATMENT

Irradiation in any form is usually without benefit as the tumor tissue is radioresistant. The treatment of choice for malignant melanoma of the choroid is enucleation and the use of radiation is limited to rare instances of tumor in an only useful eye. In performing this operation caution should be taken to avoid dissecting into the capsule around an extraocular extension of the tumor and a long optic nerve stump should be obtained at the time of enucleation.

DISCUSSION

In our series, the tumor composed of the spindle-cell type showed the highest incidence. There was a slight preponderance of females over males and the majority of patients afflicted with malignant melanoma were in the sixth and seventh decades of life. The youngest patient was 31 and the oldest 81 years of age.

Twelve of the cases were correctly diagnosed preoperatively and the remaining two were declared as glaucoma on clinical grounds. Three of the patients in our series have died of generalized metastases, death having occurred from 21 to 44 months after enucleation. Of the remaining 11, 10 are alive and well, one having died of other causes. In those who died of metastases, two had tumors of the spindle cell variety and the other was of the mixed cell type. In an additional five cases where enucleation was performed, malignant melanoma was suspected clinically but none was found. Histologic studies verified the following conditions:

1. Retinal detachment with cyclitic membrane.
2. Retinal detachment and chronic enophthalmos (fig. 3).
3. Vitreous hemorrhage, blood staining of the cornea, glaucoma, cataracts and uveitis (fig. 4).
4. Kuhnt-Junius disciform macular degeneration (fig. 5).
5. Retinal detachment, cyclitis and glaucoma.

All of these cases required enucleation because of pain and poor vision, in addition to the possibility of an intraocular malignant tumor.

We wish to emphasize that the occurrence of malignant melanomas is much greater in blind, painful eyes than in normal, healthy eyes, and we feel that a blind eye which becomes painful should be removed because of the possibility of a hidden tumor. We also

feel that a melanotic mass in the choroid which is changing in size, with no evident reason, such as a uveitis, should be consid-

ered as a malignant melanoma until proven otherwise.

2040 West Wisconsin Avenue (3).

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CORNEAL FORCEPS*

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The general trend in ophthalmic surgery is to use finer and more delicate instruments. This trend is natural as techniques become more refined.

The following forceps was designed primarily for corneal work and has proven to be extremely useful for this purpose. While

having very delicate teeth and fine balance, it is, nevertheless, a sturdy instrument which has withstood repeated usage and sterilization.

The forceps is actually a modification of the Katzin-Barraquer forceps employing a Kirby instead of a Gill handle (fig. 1). The teeth are 0.5 mm. in length, angulated at a 45-degree angle and are set one against two. Behind the teeth is a suture platform which is 7.0 by 0.6 mm.

The instrument is manufactured by the Storz Instrument Company of Saint Louis, Missouri.

* From the Division of Ophthalmology, Baylor University College of Medicine.



Fig. 1 (Girard). A forceps for fine corneal work.

A DEVICE FOR CENTERING CORNEAL GRAFTS*

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New York

Although several instruments have been designed to simplify the procedure, the centering of corneal grafts remains a problem. A glance through the illustrations of any article on keratoplasty will show a number of cases in which the technical success of the graft is marred by the poor cosmetic and optical effect of an off-center graft.

Most instruments now available for this purpose rely on centering over the pupil.

*From the laboratory of The Eye Bank for Sight Restoration, Inc., Manhattan Eye, Ear and Throat Hospital.

This is difficult in cases with central scarring so dense that the pupil is not clearly visible. Instruments designed to mark the cornea are not always sharp enough to mark a soft cornea and then, too, the marks are out of sight when the trephine is in place, or nearly so.

We have overcome most of these difficulties by devising a disc, cut from gelfilm, which is centered in relation to the limbus. The outside diameter of the disc is 10 mm. and the hole in the center is 5.0, 6.0, or 7.0 mm., according to the desired size of the graft.

In the operating room the discs are sterilized in alcohol, then soaked for about five minutes in normal saline to increase their pliability. After this soaking, the disc is al-

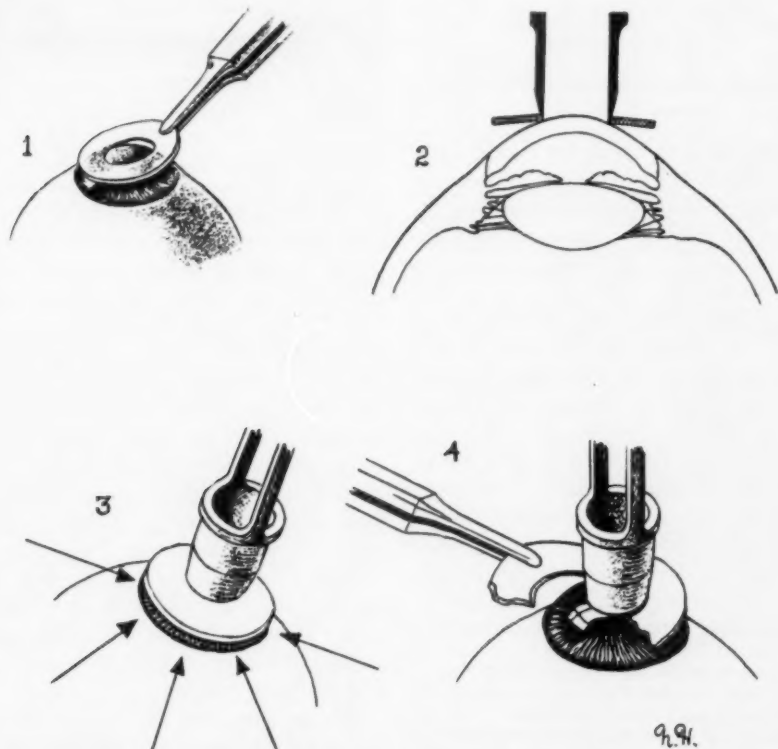


Fig. 1 (Martinez). A device for centering corneal grafts.

lowed to dry a little, since it will mold and adhere to the cornea better if both the disc and the cornea are a little dry.

The disc is then placed on the cornea, using the limbus as a guide. The trephine is placed firmly on the cornea through the central hole. When the trephine is in place, the disc can be grasped with forceps and a slight tug will break the rim of gelfilm so that it can be lifted away without removing the trephine after its initial placement.

This device has two great advantages in that it is simple to construct and easy to use. We have found it superior to other centering devices and more accurate than centering by sight alone.

210 East 64th Street (21).

A USEFUL STRETCHER*

FOR TRANSPORTATION OF THE INTRAOCULAR
SURGICAL PATIENT

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The purpose of this report is to describe a stretcher which has been of great value in transporting patients from the operating table following surgery. It has been used for all patients undergoing intraocular surgery where it is of the utmost importance that they be as immobile as possible and not be subjected to stresses while being moved. Also, whenever general anesthesia is used, this stretcher makes the transportation of the recovering patient extremely easy. It is certain that this stretcher could be used extensively in any surgical operating room, especially in hospitals where the patient's bed is not used as the operating table. Its use could be extended to moving the medicated senile or infirm patient from the bed to the operating room; also, in the transportation of the

* From the Ophthalmology Branch, EENT Service, U. S. Naval Hospital. The opinions or assertions expressed herein are those of the writer and are not to be construed as official or as necessarily reflecting the views of the Medical Department of the Navy or the Naval Service at large.

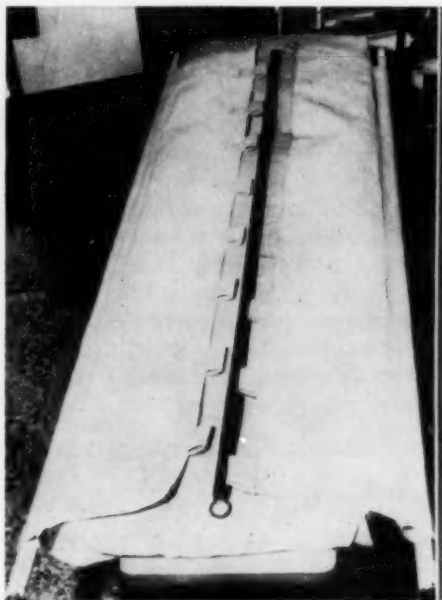


Fig. 1 (Wuest). Stretcher assembled.

comatose patient or one suffering from trauma to minimize handling and stresses.

The stretcher consists of two pieces of heavy canvas, 15 in. wide by 80 in. long; two light metal or wooden stretcher poles; and finally, a strip of stainless steel 1.0 in. wide by 80 in. long, with a metal ring at one end (fig. 1). The canvas has a continuous loop on the outer long edge, through which a stretcher pole can be placed. The center long edge has eight two-in. loops of heavy canvas, spaced about 10 in. apart. These loops are placed on the second piece of canvas so they can alternate with the loops of the first. The long metal strip can be threaded through these alternate loops of the canvas, thus making a full stretcher (fig. 1). It is recommended that the metal strip be of chrome-plated stainless steel or any other polished, smooth metal, since these slide more easily and facilitate removal.

For surgery, the assembled stretcher is placed on the operating table with the poles removed. The ring in the metal strip should

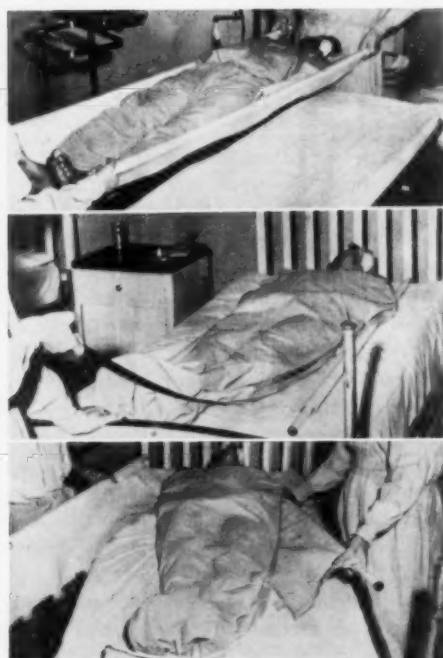


Fig. 2 (Wuest). (Top) Patient being lifted from operating table to conveyance. (Middle) Removal of the center metal strip from the stretcher with the patient in his bed. (Bottom) Removal of the stretcher halves.

be at the foot of the stretcher. The usual drawsheets and head supports are placed on the stretcher. Following surgery, the stretcher poles are put into place and the patient is easily and comfortably moved to a guernsey or other similar wheeled conveyance. He is just as easily moved from this to the bed. The stretcher is removed from under the patient by pulling the metal strip from the loops and then by moving out the canvas sections from the side, leaving the patient on the drawsheet in the bed (fig. 2).

The use of this stretcher obviates any straining by the patient in being moved, since he is not subjected to irregular pulling and lifting. It also reduces the work required of surgical assistants in transporting patients. The surgeon can be assured that the patient is being moved without stress. This

is naturally of the utmost importance following cataract, glaucoma, and retinal detachment surgery, but is comforting in all ophthalmic surgery.

U. S. Naval Hospital.

ACKNOWLEDGMENT

This apparatus was designed by Lieut. Cmdr. Helen M. Chaney (NC) U.S.N., the former EENT surgical nurse at this hospital, who has kindly permitted me to describe the stretcher.

TOPICAL FLUDROCORTISONE (9-ALPHA FLUOROHYDROCORTISONE) IN OPHTHALMOLOGY*

CESAR GONZALEZ, M.D.

Durham, North Carolina

Successful management of diverse ophthalmic lesions requires control of local inflammation. The inflammatory response readily tolerated by other tissues may have a disastrous effect on the eye and on visual acuity. The ability of topically applied corticosteroids to minimize ocular inflammation involving the anterior segment is well recognized.¹⁻⁶ Regardless of the infectious, allergic or traumatic nature of the ocular lesions, capillary permeability and cellular exudate are reduced and granulation, fibrosis and neovascularization minimized by the topical application of steroids. Of course, corticosteroids cannot be effective where the inflammatory process has already produced fibrosis and extensive neovascularization. When concomitant local infection exists or threatens, protection should be afforded by the local instillation of properly selected antibiotics.

Several investigators have reported favorable experience with fludrocortisone for anterior segment lesions.^{1,3,5,6} It has proved

* From the Ophthalmological Division, Duke University. The 0.1-percent Florinef (Squibb fludrocortisone) and 0.1-percent Florinef-S (Squibb fludrocortisone with 2.5 mg. neomycin and 0.25 mg. gramicidin per ml.) ophthalmic preparations were supplied through the courtesy of Dr. J. T. Groel, The Squibb Institute for Medical Research, New Brunswick, New Jersey. They represent the soluble hemisuccinate salt of fludrocortisone.

effective at 1/10th to 1/20th the concentration of hydrocortisone in the same type of inflammatory eye disorders.¹ A prompt anti-inflammatory action in both allergic and non-allergic disease has been attributed to this compound in many hundreds of patients over a period of more than three years.⁶ Topical use of fludrocortisone in the eye has been reported to produce no deleterious local or systemic reactions.³

Further experience with Florinef and with Florinef-S in both suspension and solution in many clinically important ocular diseases is presented in this report.

METHODS

Ophthalmic preparations containing fludrocortisone in 0.1-percent concentration or, for the prevention or control of infection, this amount of corticoid combined with 2.5 mg. neomycin and 0.25 mg. gramicidin per ml. were employed for various ocular disorders at the Ophthalmological Division of the School of Medicine of Duke University. The combination of neomycin and gramicidin provides a wide spectrum of activity against those gram-negative and gram-positive bacteria most often responsible for superficial eye infections. Dosage consisted of instillation of one or two drops from every

two hours to four times daily. According to patient response, treatment was administered for as long as six weeks.

RESULTS

A series of 121 patients, both hospitalized and ambulatory, were treated with either plain fludrocortisone (31 cases) or fludrocortisone with neomycin and gramicidin (90 cases). The duration of the ocular pathology ranged from three weeks to as long as 15 years. Fludrocortisone drops were employed to control inflammation as manifested by redness, irritation, tearing, discharge, and photophobia. Treatment was limited to the control of acute and active processes in both self-limited disease and exacerbations of chronic disease. The inflammatory diseases treated involved the eyelids, conjunctiva, and uveal tract, as well as postoperative reactions.

Two patients, one with episcleritis and one with iridocyclitis and episcleritis, had previously been subjected to local corticosteroid therapy without satisfactory results and one patient had been treated with a corticosteroid plus antihistamine without significant improvement.

A patient with chronic simple glaucoma and another with secondary glaucoma had

TABLE 1
DISTRIBUTION OF CASES AND RESULTS OF THERAPY WITH FLORINEF

Diagnosis	Number of Patients	Results	
		Good to Excellent	Fair to Poor
Conjunctivitis, follicular	4	4	0
Conjunctivitis, vernal	1	1	0
Conjunctivitis, allergic	1	1	0
Blepharoconjunctivitis with superficial keratitis	1	1	0
Episcleritis with keratoconjunctivitis	1	1	0
Keratoconjunctivitis with superficial corneal ulcers	1	0	1
Keratitis	1	1	0
Iridocyclitis with episcleritis	1	1	0
Corneal wound, hyperemia, multiple foreign bodies	1	1	0
Corneal laceration and sympathetic ophthalmia	2	1	1
HypHEMA, traumatic	1	1	0
Iritis	3	2	1
Uveitis	4	4	0
Postoperative reactions: cataract extraction, glaucoma, pterygium	9	9	0
TOTALS	31	28 (90.3%)	3 (9.7%)

TABLE 2
DISTRIBUTION OF CASES AND RESULTS OF THERAPY WITH FLORINEF-S

Diagnosis	Number of Patients	Results	
		Good to Excellent	Fair to Poor
Conjunctivitis, follicular	2	2	0
Conjunctivitis, vernal	2	2	0
Conjunctivitis, allergic	4	4	0
Conjunctivitis, bacterial	4	4	0
Conjunctivitis, mixed etiology	1	1	0
Blepharoconjunctivitis with punctate keratitis	1	1	0
Blepharoconjunctivitis	1	1	0
Iridocyclitis	2	2	0
Keratitis	4	3	1
Keratoconjunctivitis, phlyctenular	1	1	0
Episcleritis	2	1	1
Corneal ulcer	2	2	0
Corneal opacity with inflammation	1	1	0
Iritis	13	13	0
Uveitis	13	11	2
Papillitis	2	2	0
Vitreous abscess	1	1	0
Glaucoma, chronic	1	1	0
Corneal dystrophy and keratitis	1	0	1
Sympathetic Ophthalmia	2	2	0
Postoperative reactions: cataract extraction, glaucoma, retinal detachment, foreign body removal, iridencleisis	30	29	1
TOTALS	90	84 (93.4%)	6 (6.6%)

been treated with a carbonic anhydrase inhibitor and pilocarpine prior to cataract extraction and the administration of fludrocortisone. Concomitant with topical fludrocortisone, six patients were given systemic corticosteroids and in four cases systemic antibiotic therapy was considered desirable. Results of therapy are presented in Tables 1 and 2.

A good to excellent response was observed in 28 (90.3 percent) of 31 cases treated with plain fludrocortisone drops. Prompt and often dramatic relief of itching and burning and resolution of inflammation were seen in the majority of these cases. Lacrimation and photophobia present prior to therapy were frequently eliminated. There were no indications of adverse local or systemic reactions to the plain fludrocortisone.

The fludrocortisone combined with neomycin and gramicidin was employed where added protection against secondary infection was considered desirable. A total of 90 patients, some previously treated according to diagnosis with systemic corticosteroids, anti-

biotics, antihistamines, vasoconstrictors, and a carbonic anhydrase inhibitor, received the fludrocortisone-neomycin-gramicidin drops. Systemic corticoids were simultaneously given to 18 patients in this series.

A good to excellent clinical response was observed in 84 cases (93.4 percent). Rapid and complete clearing of four cases of bacterial conjunctivitis was accomplished. There was no recurrence of the infection in any of the patients.

In acute inflammatory or allergic conditions, the preparation acted quickly and effectively. Postoperative cataract reactions, traumatic iritis and uveitis were often dramatically controlled and, in almost all instances, subsided with continued treatment.

This corticosteroid-antibiotic combination was generally well tolerated and no significant manifestations of local or systemic intolerance were noted even after weeks of use. A slight burning sensation of brief duration after instillation of the drops was experienced by six patients in the group.

DISCUSSION

Experience with ophthalmic preparations of fludrocortisone and of this corticoid combined with neomycin and gramicidin demonstrated that acute inflammatory or allergic conditions of the anterior segment of the eye were rapidly and effectively suppressed. Preservation of structural integrity and, as a consequence, visual acuity is frequently possible through corticosteroid inhibition of fibrosis and neovascularization on an inflammatory basis. The addition of antibiotics to fludrocortisone was preferred, in the majority of cases treated, for protection against secondary bacterial infection.

Although the use of corticosteroids and corticosteroid-antibiotic combinations in corneal disease is sometimes hazardous due to the possibility of secondary fungal infection this did not occur in this series. When the keratopathy was complicated by neovascularization, notable diminution in the intensity of the vascular reaction was obtained.

Excellent therapeutic results were achieved during this study in certain severe, chronic diseases of the eye. Even in granulomatous uveitis, fludrocortisone with neomycin and gramicidin effected a slow but constant therapeutic response. In some instances, the improvement persisted after medication was withdrawn for several days. Perhaps fludrocortisone is stored in some

manner and only gradually absorbed into ocular tissues.

SUMMARY

Ophthalmic preparations of fludrocortisone and of the corticoid combined with neomycin and gramicidin were employed in a series of 121 patients with inflammatory or allergic eye diseases. Of 31 cases treated with fludrocortisone, a good to excellent response was achieved in 28 or 90.3 percent. With fludrocortisone plus neomycin and gramicidin, a good to excellent response was obtained in 84 of 90 patients, or 93.4 percent. Both preparations were generally well tolerated, although six patients experienced a slight burning sensation of brief duration after instillation of the fludrocortisone-antibiotic combination. With this preparation, four cases of bacterial conjunctivitis cleared and no occurrence of secondary bacterial infection was observed in this series. The added protection against bacterial infection provided by fludrocortisone and antibiotics recommends its use in larger groups of patients. Both formulations, were however, considered superior for use in corticoid-responsive ocular disease. Relatively long-term use is not likely to produce local or systemic allergic reactions or significant electrolyte disturbance.

Division of Ophthalmology.

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OPHTHALMIC RESEARCH

EDITED BY FRANK W. NEWELL, M.D.

950 East 59th Street, Chicago 37, Illinois

Abstracts of papers presented at the meeting of the Western Section of the Association for Research in Ophthalmology, Inc., University of California, San Francisco, November 19 and 20, 1959.

Leonard Christiansen, M.D., and A. Ray Irving, Jr., M.D., *Co-Chairmen*

Daniel G. Vaughan, *Section Secretary*

Patterns of competitive interaction for brainstem evoked eye movements in cats. Jane E. Hyde, Ph.D., Department of Physiology, U.C.L.A., Los Angeles 24.

Earlier work in the feline *encéphale isolé* has demonstrated that electric stimulation in many areas of the brainstem will cause the eyes to move to a consistent conjugate position. The anatomic location of the stimulated site is the main determinant of the direction of the evoked movement. The present study utilizes stimulation techniques in an effort to determine relative functional dominance of different parts of the brainstem in the co-ordination of eye movements.

The areas tested were the left and right superior colliculi, the dorsal tegmentum of the midbrain, and the medial reticular substance of the medulla. Individual stimulation of the midbrain sites yields contralateral conjugate deviations, that of the medulla evokes ipsilateral responses. Pairs of opposing brainstem sites, individually yielding movements of the eyes to right and to left, have been stimulated simultaneously.

Three major types of responses are found from analysis of motion pictures of the eye movements evoked by such simultaneous stimulation: (a) the eyes move to a final position intermediate between the goals of either site alone; (b) the eyes oscillate between the goals of the two sites; (c) simultaneous stimulation evokes a movement identical to that evoked from one of the sites alone. The first two patterns of competitive interaction suggest relative functional equivalence of the two sites tested; the third indicates dominance of one over the other.

The different patterns are correlated with the anatomic location of each tested site. Thus an intermediate final ocular position resulted from simultaneous stimulation of sites in the left and right superior colliculus. Combined stimulation of right superior colliculus and left midbrain tegmentum evoked an intermediate position closer to the goal of the tegmentum than of the colliculus. With simultaneous stimulation of the left medulla and the left midbrain tegmentum, the eyes either moved to the left or oscillated between left and right. Simultaneous stimulation of the right superior colliculus and the right medulla caused a response

identical with that due to stimulation of the medulla alone.

By the technique used, the order of relative functional oculomotor dominance of the three areas tested is: medial reticular substance of medulla, dorsal midbrain tegmentum, and superior colliculus.

Observations on experimental trachoma produced in cynomolgus monkeys by yolk sac culture of trachoma elementary bodies. P. Thygeson, M.D., C. Dawson, M.D., and M. Okumoto, M.A., Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine, San Francisco 22.

In the history of trachoma research, monkeys have been relatively unsatisfactory test animals for the detection of trachoma virus in conjunctival scrapings or other tissue suspensions. The experimental disease has had an insidious onset and minimal inflammatory signs, and has healed spontaneously in a few months without scars or pannus and without ever presenting demonstrable inclusion bodies in epithelial scrapings. The susceptibility of these animals to spontaneous folliculosis has been a complicating factor.

Recently a strain of elementary body virus from a typical case of trachoma in a white Californian was propagated in the yolk sac of embryonated eggs (Hanna et al., *Science*, in press). This virus, upon inoculation into *M. cynomolgus*, produced a well-defined sequence of eye lesions. From two to seven days after inoculation of the eye there was an acute onset with marked inflammation and abundant inclusions. Neither scars nor pannus have developed, but the experimental disease has been regularly producible and the epithelial scrapings from it have presented a diagnostic cytologic picture. Confusion between this disease and spontaneous folliculosis is not a problem.

A virus isolated from a case of clinical trachoma.

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Microbiology and Ophthalmology, and Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine, San Francisco 22.

Scrapings were obtained from the conjunctivas of a patient (a 36-year-old white machinist residing in San Jose, California) with clinically typical trachoma. Numerous inclusion bodies were demonstrable. These scrapings, when injected into the yolk sac of embryonated chicken eggs, yielded a virus which has been related to the psittacosis-lymphogranuloma group. When the infected yolk sac material is inoculated into monkey eyes it produces an acute, follicular conjunctivitis, with typical inclusion bodies. The virus has been re-isolated from the infected monkey conjunctiva.

This isolation is believed to represent the first isolation of "trachoma virus" in the United States. It has been compared with similar isolations by Snyder and others from Saudi-Arabia.

Trachoma in Mexican agricultural workers (barceros) entering the United States. Chandler R. Dawson, M.D., Communicable Disease Center, U. S. Public Health Service and Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine, San Francisco 22.

Trachoma recently has been found to be prevalent among the indigenous Mexican population in certain agricultural areas of southern California. Because a trachoma control program is being contemplated, Mexican nationals entering this country to do seasonal agricultural labor were screened for trachoma to find if these men were a potential source of infection for the indigenous Mexican population. This report deals with the results of these trachoma surveys. Since these men come from all parts of Mexico, it also was possible to draw some conclusions about the geographical distribution of trachoma in that country.

Clinical surveys for trachoma were carried out at the United States Public Health Service medical units of Bracero Reception Centers where Mexican agricultural workers are screened medically before being allowed to work in the United States. During the survey the conjunctiva and cornea of each man was examined with the aid of a binocular loupe and hand illuminator and a small number were examined with a slitlamp to confirm the corneal changes of the disease and to diagnose doubtful cases. The findings in each instance were entered on a form along with the individual's name, age, state of residence and birthplace.

It was found that less than one percent had active trachoma (stages I, II, or III) although 19.9 percent had signs of healed trachoma (stage IV). This is not an unusual ratio of infectious to healed cases, since adult males are usually least likely to have active trachoma in endemic areas. The highest prevalence occurred in men from the

northern states of Sonora, Sinaloa, Nuevo Leon and Tamaulipas, with rates of over 50 percent; comparatively high rates (between 20 and 30 percent) occurred also in the northern states of Durango, Coahuila, and San Luis Potosi. The age-specific rates revealed that all age groups from Sonora, Sinaloa, Nuevo Leon and Tamaulipas had rates of around 50 percent, while only the older men from other parts of Mexico showed evidence of trachoma infection; this may indicate that the disease has died out except in the northern states.

Organ type tissue culture of ocular tissues. William van Herick, M.D. and Chieko Yoneda, Department of Ophthalmology, University of California, San Francisco 22.

Normal and malignant ocular tissues were cultured as an organ type tissue culture. The object of these experiments was threefold: (1) to determine survival period of these tissues, (2) to obtain a pure cell line by differential cell survival using this method, that is, pieces of ocular tissue were maintained in the medium to their end-point of survival in the hope that a certain type of cell would survive longer than others, thereby a pure cell line would be obtained, and (3) conversely to obtain organ type of tissue growth in a differentiated form.

Two methods were used for suspending tissues: (1) rayon acetate cloth coated with silicone and (2) human vitreous. The loose textured rayon acetate cloth was cut into squares 1.5 cm. and coated with silicon. Small pieces of tissues were placed on the cloth and floated in the tissue culture medium. Vitreous was obtained from eye-bank eyes. Pieces of tissue were suspended on the vitreous and the tissue culture medium was added. The medium was changed at regular intervals.

Tissues were destroyed at regular intervals of time and histologic sections were made. They were also tested for their viability and type of cellular outgrowth by the usual plasma clot tissue culture method. Ocular melanomas, retinoblastomas, normal ciliary body, iris and retina were treated in this manner.

Of interest in these experiments has been the ability of melanoma, iris and ciliary body tissues to be maintained and to survive for 150 days by these methods. Recent experiments indicate that maintenance and survival of tissues were longer when tissues were submerged in culture medium than when they were exposed to air.

As yet, fibroblasts, melanocytes, and melanoma cells appear to survive longer than other types of cells but we have not been able to obtain a pure cell line. Histologic sections of the tissues revealed central necrosis with a peripheral area of healthy looking cells. Rarely has there been any increase in size of tissue mass.

Experiments are now in progress in an attempt to promote differentiated growth as an organ type.

Diffusion studies and vitreous structure. Anita Suran and W. K. McEwen, Ph.D., Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine, San Francisco 22.

The structure of the vitreous body is pictured as a meshwork of fine fibrils permeated with vitreous filtrate, containing hyaluronic acid as its chief component. We were interested in sizing the interstices of the fibrous network by diffusion through it of various molecules ranging in size up to 22 millimicrons. The rate of outflow of hyaluronic acid was measured in another series of experiments. The significance of our results will be discussed in relation to the structure calculated for a simple ideal system.

Experimental hyphema in rabbits: II. The effect of acetazolamide (Diamox) on the rate of absorption. Robert M. Sinskey, M.D., and Alice R. Krichesky, A.B., University of California, Los Angeles.

In previous studies using Cr-51 tagged red cells, it has been shown that mydriatics and miotics have no detectable effect on the rate of absorption of hyphema in the rabbit. In an attempt to find a drug which could conceivably affect the absorption of red blood cells from the anterior chamber, Diamox was selected for use because of its known effect on the secretion of aqueous.

Similar animals and techniques were used for the labeling of the red cells, injections into the anterior chamber and obtaining and counting of the peripheral blood specimens as those in the study on mydriatics and miotics. Diamox in injectible form was reconstituted with sterile water so that 0.5 cc. contained the desired single dosage.

Four injections of 0.5 cc. each were made as follows: Intravenous, in the ear vein, 90 minutes before induction of the hyphema; intravenous, three hours after induction of hyphema; intramuscular, in the hind leg, seven hours after induction of hyphema; intramuscular, 24 hours after induction of hyphema.

The results show that the minimum effective dosage of Diamox is 100 mg. per injection \times 4. The maximum and optimum effective dosage, as found in this study, is 104 mg. per injection \times 4. It is quite remarkable that the dosage level has such a critical range of effectiveness, being only 4.0 mg. \times 4. Dr. Becker had found in his aqueous studies on rabbits that any dosage of Diamox below 100 mg. per initial injection was ineffective.

It is difficult to determine by this study alone why Diamox is effective in increasing the rate of absorption of red blood cells from the anterior chamber. Clinically, we observed that the absorption of hyphemas is retarded by an elevation in intraocular pressure. Perhaps by inhibiting the secretion of aqueous, Diamox allows the red blood cells to move through the trabeculae into Schlemm's canal in a more orderly fashion, whereas if the red blood cells must compete with

normal outflow of aqueous, then the absorption would be decreased. Further studies using tonometry in conjunction with tagged red cells may shed additional light on the unusual phenomenon uncovered in this study.

A comparison of the study of vasodilators by different techniques. Victor G. Fellows, M.D., and Jerome W. Bettman, M.D. Department of Ophthalmology, San Francisco-Stanford Hospital. Supported by National Institutes of Health Grant No. USPHS B2634.

We have previously reported the use of P^{32} in the measurement of changes in the blood volume of the choroid and retina in the cat. The technique is summarized: 10 cc. of blood were withdrawn from a cat, heparinized, incubated at 37°C. with 2.0 mc. of P^{32} for two hours, spun down, washed three times, resuspended and reinjected into the blood vessel. The P^{32} is confined to the erythrocytes, these are confined to the vascular tree and hence the radioactivity is an indication of the volume of blood reflected by the Geiger-Müller probe.

We systemically tested agents that might influence the blood volume in the cat and found the following to produce marked and consistent increase in blood volume: CO_2 by inhalation, aminophyllin by retrobulbar injection, Priscoline by retrobulbar injection, nicotinic acid by retrobulbar injection, nicotine by inhalation or intravenous injection and paracentesis.

The present work was performed to explain the difference in results with that of Leopold and Wudka. We felt it might be because we were studying different blood vessels: Leopold saw only the larger choroidal vessels through his microscope; we obtained most of the response of radioactivity from the choriocapillaris when using our P^{32} technique. We were also aware that the difference might be due to either functional or anatomic differences in the cat and the rabbit.

In an attempt to answer this problem we performed scleral windows on cats, but the amount of choroidal pigment made the results impossible to determine. We therefore administered to rabbits the agents that had produced definite increase in blood volume in cats, and studied the results by the P^{32} technique.

A comparison of the effect on blood volume in the cat and rabbit follows: 10-percent CO_2 by inhalation produced a marked increase in blood volume in cats; it had no effect on rabbits (eight trials, five animals). Aminophyllin by retrobulbar injection resulted in a marked and prolonged increase in blood volume in cats; it had no consistent effect on rabbits (one slight increase, two no effect, three slight decrease, two unreliable). Priscoline by retrobulbar injection definitely increased the blood volume in the cat eye, it had no effect in rabbits (six eyes). Nicotinic acid by retrobulbar injection moderately increased the blood volume in cats, it had no consistent effect in rabbits (four animals). Paracentesis resulted

in an interesting series of results when different amounts of aqueous were withdrawn. Withdrawing a minimal amount of aqueous (approximately 0.05 cc.) resulted in a slight increase in blood volume for a short time in cats. It had no effect on rabbits. Withdrawing a moderate amount of aqueous (0.2 cc. in each animal) resulted in a marked effect of moderate duration in cats, and no effect in rabbits. Withdrawing a maximal quantity of aqueous (0.8 cc.) in the cat produced a marked and prolonged effect. The withdrawal of a maximal amount of aqueous in a rabbit resulted in an increase in blood volume in six out of seven animals and varied from 25 percent more to twice as fast.

It is concluded that the difference in response obtained by Leopold and his group using the scleral window technique on rabbits and the results obtained by the P^m technique on cats is due to a difference between cats and rabbits and not due to difference in response of the larger choroidal vessels as opposed to the choriocapillaris.

The purification of hyaluronidase from bovine testes. S. Rodman Irvine, M.D., and S. M. Mozersky, Ph.D., Division of Ophthalmology and Department of Physiological Chemistry, University of California, Los Angeles.

The purification of the enzyme hyaluronidase from bovine testes has been the object of sporadic efforts begun almost 30 years ago (McClean, D., *J. Path. & Bact.*, **33**:1045, 1930). In the last several years our techniques in the field of protein separations have improved considerably so that it seemed profitable to investigate the possibility of further purification of the enzyme.

A preliminary examination of existing methods showed that the procedure of Hahn (Biochem. Ztschr., **315**:83, 1943), although quite lengthy, was also quite reliable, in contrast to some of the other published methods. A systematic investigation of Hahn's procedure was undertaken, with the following results:

1. The extraction of hyaluronidase from ground testes with an equal volume of 0.1 M acetic acid is complete in 15-20 hours. The enzyme appears to be little affected by proteolytic enzymes present.

2. Sixty-percent saturation with ammonium sulfate suffices for complete precipitation of the enzyme.

3. The concentration of sodium chloride (in the presence of copper sulfate) for the removal of contaminating protein can profitably be raised (from 50-percent saturation) to 71-percent saturation, without significant loss of enzymatic activity.

4. The lead acetate procedure of Hahn gives variable results, the variation apparently depending on the previous history of the sample. Preliminary determinations of the optimal ratio Pb⁺⁺/protein and of the optimal concentration of protein appear to be necessary in every case for the best results.

Products obtained by Hahn's procedure (modified) were used as starting materials for further purification studies. For these two ion exchange resins proved useful, the anion exchanger diethyl-amino-ethyl cellulose (DEAE-cellulose) and the cation exchanger Amberlite IRC-50 (CG-50). It was found possible to remove much contaminating protein from the enzyme by adsorption of the former with a column of DEAE-cellulose at pH 7.0 (0.0050 M phosphate). Under these conditions the enzyme is not adsorbed.

Amberlite IRC-50 at pH 6.0 (0.050 M. phosphate) binds hyaluronidase very tightly (Rasmussen, P.S.: *Biochemica & Biophysica Acta*, **14**:567, 1954). This fact was utilized for the concentration of the enzyme from large volumes of solution, with the simultaneous removal of much contaminating protein. The enzyme was first adsorbed to a column of the resin, and washed thoroughly. For elution the resin was extruded from the glass cylinder, suspended in 0.50 M sodium chloride containing 0.033 M dibasic sodium phosphate (buffer C), and brought to pH 7.7 with ammonia. The resin suspension was poured back into the cylinder and the effluent collected. The column was then washed with additional buffer C and the effluent pooled with the previous effluent. Salts were removed by dialysis and a dry product obtained by lyophilization.

The sequential use of DEAE-cellulose and IRC-50 was found to yield a product with a specific activity seven to 10 times that of the starting material, which had been fractionated with ammonium sulfate, copper sulfate, sodium chloride, and lead acetate, according to Hahn.

Recently conditions have been found under which the enzyme is adsorbed to DEAE-cellulose. This fact may permit high-resolution chromatography of the enzyme on this resin. Such a procedure is now under investigation.

Dog tear proteins and egg white lysozyme. Seymour R. Roberts, D.V.M., and Olive F. Erickson, M.D., Stanford University School of Medicine, San Francisco 15.

There are four major components in dog tears using the standard electrophoresis apparatus: (1) Lysozyme is present in a very few. The two most consistent bands are: (2) the peak which occurs in the mobility range half-way between gamma and beta of blood serum. It is a broad band and overlaps both of these areas. The (3) component, also a broad peak, which occurs approximately at alpha 2. (4) The protein in the albumin zone, usually is either absent or very low. The protein concentration tends to be much lower than human tears and the rate higher.

Egg white lysozyme. This study was done in co-operation with Dr. Samuel Lepkowsky of the University of California, Department of Poultry Husbandry, Berkeley, and Dr. I. M. Sharon, D.D.S., 3475 California Street, San Francisco.

For a period of six weeks eggs were obtained from four hens which were given increasing

atropine doses starting at 1.0 mg. orally per day and gradually increasing the daily dose to 64 mg. The percentages of protein components were determined in the same manner as for tear proteins. The purpose of this experiment was to study lysozyme production in the hope that we might find a useful human application. To our surprise, after an initial drop, the lysozyme levels, even on tremendous doses of atropine, tend to return to their original values.

The effect of corticosteroids on herpes keratitis in the rabbit. M. Okumoto, E. Jawetz, M.D., and M. Sonne, Francis I. Proctor Foundation for Research in Ophthalmology and the Department of Microbiology, University of California School of Medicine, San Francisco 22.

The corticosteroids are used by ophthalmologists for a variety of ocular disorders with very favorable results in many cases. Their use in herpes simplex keratitis, however, has not been very favorable. The detrimental effects of the steroids in herpetic keratitis are felt to be due to an increased proliferation of the virus in the cornea. This hypothesis was explored by a series of experiments aimed at measuring the virus level in the corneas at various times following the inoculation of the herpes virus into steroid treated and untreated rabbit corneas. The PH strain of herpes virus in the form of a 20-percent mouse brain suspension was used. Colored rabbits were given subconjunctival prednisolone or hydrocortisone for a period of five days, and on the second day these rabbits as well as normal control rabbits were inoculated by scratching the corneas of both eyes with the virus suspension. This strain of herpes produced corneal lesions which could be observed as early as the following day. The clinical course of the keratitis was carefully observed and beginning about the eighth day following the virus inoculation, the steroid effect was noted. The corneas treated with the corticosteroids became progressively worse, whereas the control eyes gradually healed. At regular intervals following the virus inoculation, two steroid treated rabbits and two control rabbits were killed and their corneas assayed for virus content. The results of the corneal titration performed by intracerebral injections of the corneal emulsions into young mice showed a rapid rise in virus titer with 24 hours. This level was maintained for approximately four to five days, and then gradually dropped until the tenth day, after which no virus could be demonstrated.

It was interesting to find that there were no significant differences in the level of virus concentration between the steroid treated and untreated control eyes.

The destructive influence of the steroids in herpetic keratitis is therefore not attributable to an increased proliferation of the herpes virus. It is suggested that the detrimental role of the corticosteroids may be due to interference with the

normal reparative processes or a direct action on the structural or physiologic integrity of the corneal stroma which might facilitate the damaging action of the herpes virus in the cornea.

Experimental herpes simplex uveitis. Samuel J. Kimura, M.D., University of California School of Medicine, San Francisco 22.

Uveitis was produced in rabbits by injecting herpes simplex virus into the anterior chamber. The virus produces an immediate severe uveitis which subsides gradually in 10-12 days. If only one eye is injected with the virus then the fellow eye develops a uveitis in 11-13 days. An attempt was made to isolate the virus from both the inoculated and the uninoculated eyes that develop uveitis. The unmasking technique utilizing tissue culture methods was successful in reisolating the virus from various tissues of the eye. The virus could not be isolated from the aqueous humor even one day after inoculating the virus into the anterior chamber.

Experimental tonometry and tonography on rabbits: Limitations in the study of the facility of outflow. Ruth Heuscher, M.D., and Milton Flocks, M.D., Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine, Stanford Hospital, San Francisco 22. This investigation was supported by research grant B-873 (C3), United States Public Health Service.

In our hands, intraperitoneal pentobarbital sodium combined with local anesthesia is the most satisfactory form of anesthesia in rabbits for tonometric and tonographic experimentation not extending beyond two hours at a time.

In rabbits a mean variation in tension of less than 2.0 mm. Hg cannot be considered significant with any indentation type tonometer. With the electronic tonometer a mean variation of 5.0 mm. Hg only can be considered significant due to the lability of the animal eye.

A correct evaluation of the facility of outflow and the flow can be made only when careful consideration is given to the time in minutes after an experimental interference on one eye, when the second tonography is performed on that eye.

If a rabbit eye suffers a sudden change of intraocular pressure through an outside agent, self-regulating changes affecting the values of the facility of outflow and the flow occur in the same eye. No significant consensual change following compression or retrobulbar injection of Novocaine was observed. No related consensual change has been noted.

Because of the many factors involved and particularly that of the difference in the behavior of the scleral rigidity of rabbits with changes in intraocular pressure as compared to that of man, one must exercise great caution in applying data derived from tonography on rabbits to questions regarding human physiology.

Congenital posterior ectasia of the sclera in collie dogs. Seymour R. Roberts, D.V.M., Department of Ophthalmology, Stanford University, San Francisco.

A congenital eye defect of collie dogs occurring in a breeding kennel is described. The most consistent finding was attenuation of the posterior scleral wall. In some eyes there was ectasia at the posterior pole and cavitation of the head of the optic nerve. In adult animals, retinal detachment and intraocular hemorrhage were common sequelae.

The principal group consisted of the breeding stock, retired stock and pups from one kennel. Twenty-four dogs from the principal group were examined ophthalmoscopically. Nine of them were killed and their eyes were examined grossly and histologically. Eighteen other collie dogs, sporadic cases, were examined ophthalmoscopically.

With the exception of one eye in which ectasia of the thinned posterior scleral wall had already occurred at age three months, the eyes of six pups showed attenuation of the sclera, the choroid, and the tapetum. In three older dogs, ectasia of the posterior scleral wall had occurred. If this represents a later stage of the same process as seen in three-month-old pups, normal growth processes may explain the events that lead to ectasia.

A number of dogs presented the ophthalmoscopic appearance of craterlike holes in the optic disc. Two eyes in this series showed holes in the optic nervehead histologically. It was theorized that such holes may be a part of a widespread defect, the intraneural counterpart of a general scleral failure.

The cause of the anomaly may be a mesodermal arrest with particular attenuation of the sclera. It is characterized by a general, rather than a segmental, failure, as seen in coloboma. Abnormal differentiation of the optic cup, with resulting attenuation of the ocular tunics, appears to be basic to the defect. Ectasia initiates degenerative changes which culminate in retinal detachment and/or intraocular hemorrhage. Micro- and macrocystoid degeneration, or tears in the retina, ultimately result in retinal detachment. Intraocular hemorrhage may occur from rupture of choroidal or retinal vessels as they are stretched over ectatic parts.

Study of pedigrees indicates that the defect is inheritable. Most of the data appear to satisfy the criteria of recessive inheritance.

There are striking similarities between this anomaly and progressive axial myopia as seen in man. Both show enlargement of the posterior eye segment predicated on defective ocular tunics, with resulting degenerative changes in the choroid and retina.

The inbred affected stock may offer a unique opportunity for experimental surgery in the study of retinal detachment. Study of the embryologic

stages may yield information about the formal genesis of high myopia.

Coloboma of the choroid with retinal detachment.

David O. Jesberg, M.D., University of California Medical Center, San Francisco, and Charles L. Schepens, M.D., Retina Foundation and Massachusetts Eye and Ear Infirmary, Boston.

This work consists of a study of 13 cases of choroidal coloboma in humans who were seen clinically by the Retina Associates of Boston and at the Retina Service of the Massachusetts Eye and Ear Infirmary.

Of the 26 eyes, 24 were colobomatous and in 10 detachment of the retina occurred. Seven cases had surgery for detachment of the retina. Embryologically coloboma of the choroid is due to malfusion of the choroidal fissure usually with absence of the pigment epithelium and choroid in the area of the defect. The retina is malformed in the colobomatous area and there is a tendency for ectasia.

Careful study of the clinical material reveals that breaks in tissue continuity leading to accumulation of subretinal fluid may occur in the colobomatous area. These breaks are very difficult to visualize but can occasionally be seen by stereoscopic indirect ophthalmoscopy.

When obvious peripheral breaks explain the detachment, the surgical therapy should be directed to their closure. If breaks in the colobomatous area are visualized or even if not visualized and the detachment cannot be adequately explained by peripheral breaks alone, it has been found that delimiting diathermy of the colobomatous defect may cure the detachment.

Illustrative cases are discussed in detail and indicate the necessity of most careful study of these cases. The importance of stereoscopic indirect ophthalmoscopy and direct control diathermy is also emphasized.

Experimental carrageenan granuloma of the cornea: Preliminary studies. Robert P. Burns, M.D., and Richard Beighle, B.S., University of Oregon Medical School, Portland 1.

Carrageenan is a water-soluble hydrocolloid extracted from a seaplant, Irish moss. It is a strongly negatively charged polymer of sulfated D-galactose units. It has a high molecular weight and forms a highly viscous solution. Carrageenan has been found to produce a granuloma rich in collagen when injected into the subcutaneous tissues of the guinea pig. The collagen reaches a maximum amount at the end of 14 days and then atrophies to a small remnant of firm fibrous tissue at about six weeks. Chemical analysis of the carrageenan granuloma has shown that there is early production of a neutral salt soluble collagen precursor maximal in the first six days and associated with an elevation in Na_2SO_4 and hexosamine. After six days there is an increase

in citrate-soluble collagen precursor. Insoluble collagen increases rapidly in the carrageenan granuloma up to about seven to eight days and then more slowly to a maximum in 14 days. Histologically, the carrageenan granuloma has been described as production of edema followed by granulation tissue with the deposition of collagen at about 14 days. Subsequent reabsorption of the collagen occurs.

Carrageenan was injected into guinea pig and rabbit corneas and the changes produced were analyzed by various stains pertinent to connective tissue proliferation. A corneal opacity was produced which was at a maximum in 12 to 16 days and disappeared gradually over the next several months.

The first three days edema with beginning cellular invasion were the prominent changes. At six days cellular and capillary invasion had advanced and there was a suggestion of silver staining deposits with the reticulin stain and a condensation of metachromatic material in the Rinehart:Abul-Haj stain. At nine days the reticulin stain was definitely positive, and by 12 days there was a large amount of new collagen deposited in the center of the thickened cornea.

At 16 days the process reached a maximum as shown by yellow staining new collagen with the Van Gieson stain, positive reticulin stains and new metachromatic material shown by the periodic acid-Schiff and Rinehart:Abul-Haj stains. By 20 days corneal thickness began to diminish and the metachromasia of the periodic acid-Schiff and the Rinehart stain decreased rapidly. The reticulin and Van Gieson stains remained highly positive.

By 30 days the Van Gieson stain began to show pinkish coloration of the mature collagen fibers and the reticulin stain diminished in intensity. The cornea was of approximately normal thickness. Subsequently there was slight atrophy of the center of the cornea with some blood vessels remaining and the normal blue corneal stain seen with the Rinehart:Abul-Haj technique had not completely returned by 80 days.

Other experiments were done with carrageenan in producing a choroiditis to assay its effect in therapy of retinal detachment. Further studies are planned with this agent. It is considered to be a valuable technique in the study of wound healing and connective tissue metabolism.

Auto-immune uveitis in guinea pigs. Samuel B. Aronson, M.D., Department of Ophthalmology, University of California School of Medicine, San Francisco 22.

Pigmented and albino guinea pigs were immunized with homogenized homologous pigmented uveal tract and complete adjuvant (Difco) at repeated intervals. Both clinical and histologic inflammatory lesions of the uveal tract (uveitis) were produced. Skin tests for homologous uveal tract were positive in many experimental animals.

Descemet's membrane in the peripheral cornea: An electron microscopic study. Levon K. Garron, M.D., and M. L. Feeney, Francis I. Proctor Foundation for Research in Ophthalmology and Department of Ophthalmology, University of California School of Medicine, San Francisco 22.

Descemet's membrane in the peripheral portion of the human cornea presents a different electron microscopic appearance from that of the central cornea. In both areas the outer third of the membrane shows a typical banding when cut transversely. Near Schwalbe's line the membrane shows isolated areas of dense banding in the inner portion as well, and heavier areas of a rather dense ground substance. These banded areas closely resemble the clumps of banded material which occur in the trabecular meshwork. Attempts are made to correlate these various banded materials from a study of their morphologic and chemical natures. Other aspects of peripheral Descemet's membrane such as subendothelial fissures and Hassle-Henle warts are presented.

Experimental photocoagulation of the iris of guinea pigs: A pilot study. Michael J. Hogan, M.D., and Ariah Schwartz, M.D., Department of Ophthalmology, University of California, San Francisco 22.

The photocoagulator was used to produce lesions in the iris of 20 pigmented guinea pigs. The intensity and the diameter of the light beam were varied. The immediate response to the light applications was the production of visible shrinkage and coagulation of the iris stroma with pupillary distortion. In some instances marked dispersion of pigment from the coagulated iris occurred into the anterior chamber and boiling of the aqueous humor occurred. Occasional irises had explosion in the superficial stroma with an audible sound.

Two series of animals were treated. One series of five animals had coagulation at low intensity with a light beam of three-degree diameter and with the diaphragm varied from "0" at the 3-o'clock position of the midstroma of the iris to a setting of "3" at the 9-o'clock position on the iris midstroma. The second series of five animals was given coagulation at low intensity with a 0.5-degree diameter light beam, also with the diaphragm setting varied from "0" to "3" at the two different positions of the midstroma of the iris. It was found that lesser effects were obtained in the irises of the latter group of animals as determined by immediate examination. In each series of animals the eyes were enucleated after one hour, one day, four days, 14 days, and 28 days. The eyes were fixed in formalin, embedded in paraffin, sectioned serially, and stained with hematoxylin and eosin.

Histologic studies of the group of five animals receiving photocoagulation with the smaller light

beam showed minimal iris stromal changes with atrophy of the supporting layers, shrinkage of the processes of the melanocytes, with formation of round clumped cells and slight atrophy of the pigment layer. The lens in most of these animals failed to show any damage.

Clinical and microscopic examination on the group of five animals which were treated with the larger light beam showed marked coagulation of the iris in those eyes which were removed one hour after the light application. In the same eye the iris sector treated with the diaphragm setting at "0" (wide open) showed more intense iris coagulation than with the diaphragm at "3" (partly closed). The stromal cells and melanocytes showed shrinkage of their cytoplasm, rounding of the cell bodies, and shortening of the processes. Within four days all of these cells had

disappeared and a hole was present in the treated area of the iris. Cataractous changes occurred in the underlying epithelium and anterior lens cells. These changes were present in all of the animals whose eyes were removed after one hour. All animals from this time on showed cataractous changes confined to the area directly underlying the treated iris. Mild to moderate inflammatory changes occurred in the episclera, limbal tissues and ciliary body.

The histologic changes observed in all these animals varied with the intensity of the light source and the diameter of the light beam. The necrosis and the hole formation occurred only with rather intense coagulation. The lens changes were remarkable. Apparently the posterior segments of 20 eyes were not damaged by any of these coagulations.

OPHTHALMIC MINIATURE

. . . I have reached the conclusion that the character of the bibliographic citations provides an almost unfailing index of the scientific merit of a given work and of the care with which the manuscript as a whole has been prepared. If there is no consistency in mode of citation, if some volume numbers are given in Arabic and others in Roman, if the author's initials are included in one place and not in another, and if the journal abbreviations are erratic and illogical, these things suggest strongly that the author of the work is careless, and that he is probably as untidy in his habits of thought and in his laboratory experimentation as he is in handling his references.

John F. Fulton,

"The principals of bibliographic citation,"

Medicine and Writing, New York, M.D. Publications, 1956, p. 26.

SOCIETY PROCEEDINGS

Edited by DONALD J. LYLE, M.D.

CHICAGO OPHTHALMOLOGICAL SOCIETY

March 16, 1959

DR. J. VERNAL CASSADY, *President*

ORTHOPTIC SURGERY FOR AMBLYOPIA EX ANOPSIA

DR. JAMES E. LEBENSOHN stated that frequently operation on the dominant eye in esotropia with amblyopia followed by occlusion of the dominant eye will result in a functional result because of the drastic insult to the preoperative status quo. He illustrated this thesis with the case of a four-year-old child with a 70^A right esotropia and amblyopia. A standard recession-resection operation of the right horizontal recti was performed and in addition a five-mm. recession of the left lateral rectus was done. This resulted in an immediate left esotropia. However within three months vision in the previously amblyopic right eye had improved to 20/20 and in 10 months the eyes were parallel. Two years later visual acuity was 20/13, O.U., and there was demonstrable binocular stereopsis.

EYE HEALTH PROGRAM IN PUBLIC SCHOOLS

DR. LAWRENCE LAWSON, DR. ROBERT A. MCGUIGAN AND MISS IRMA FRICKE presented the program that had been developed for eye health in the public schools of Evanston, Illinois. They emphasized that such a program to be successful must be simple, economical of time, money and efficient in discovering eye defects, yet avoid the pitfall of overreferral.

Children were screened annually by a registered nurse using a standard Snellen chart at 20 ft. In addition to those failing the test, all children with obvious ocular defects were referred to ophthalmologists. Of 15,891 children, 7.3 percent were found to need

ocular care. (This is in addition to those already wearing glasses which corrected their vision to normal levels.) The false referral rate in this group was only 4.2 percent.

Discussion DR. JAMES E. LEBENSOHN:

An adequate eye health program in every school system is a consummation devoutly to be wished. That depicted in the Evanston schools is simply a primitive type of visual screening. No tests for hyperopia, muscle balance or near vision were performed. Hence only 7.3 percent were recommended for ocular attention. Statistics indicate that three times as many were disregarded who would have benefited also by eye care. Dr. Lawson cited a government study which revealed that 26 percent of grade school children require ocular attention, and referred to the report by Good and Holmes that 26 percent of children wearing glasses could not pass the screening test. Several other ophthalmologic surveys arrived at similar figures—that 25 percent of school children have significant errors of refraction and that an additional seven percent have significant ocular muscle imbalances. The Snellen test at 20 ft., valuable though it is, errs on the side of underreferral and locates but 60 percent of the students that need help. The excerpts quoted by Dr. Lawson from the St. Louis project and from the collaborators in the New England survey reflect inaccurately the true views of the authors. Actually, Scobee and his co-workers found that a high standard Snellen far test (20/20) combined with an equivalent near test secured the same number of correct referrals as the Massachusetts Vision Test, while Lancaster and his group agreed that it is preferable for school screening procedure to err in overreferrals than in under referrals. Scobee admitted that any procedure which refers half or more of the students who need care will

give a high proportion of unnecessary referrals. But he concluded it is better to give students the benefit of doubt than to neglect them. Kephart found that 500 of 2,000 pupils in grades three to 12 failed the near test, and of these failures nearly half had ranked above standard in the far test.

Though the range of accommodation in youth is high, averaging 14D. at the age of eight years, the child cannot make too much use of it because excessive accommodation is linked with excessive convergence. In near work the hyperope prefers to see indistinctly and single rather than distinctly and double. A normal child has not too much hyperopia, the modal value being 2.0D. at ages three to five, 1.0D. at ages eight to 10, and 0.5D. after 10 years of age. The refraction curve of the school population is symmetric and shows as many cases of abnormal hyperopia as of myopia when examined under cycloplegia. Children cannot sustain more than 6.0D. of accommodation. Occasionally a child with 6.0D. hyperopia will read 20/20 in the Snellen test, but his near acuity will be equivalent to 20/50 or less. The incidence of accommodative squint attains its maximum at 6.0D. hyperopia, but drops suddenly with 7.0D. hyperopia.

The initial efforts to improve visual screening by Eames in 1938 and by Albert Sloane in 1940 were enthusiastically welcomed. But the pendulum swings backward now. The hue and cry of over-referral comes particularly from the influential citizens of our wealthier suburbs. These worthies are keenly aware that glasses do not enhance appearance, social charm or athletic prowess. When dealing with hyperopia, it is hard to sell the idea in these staunch conservative strongholds that glasses normalize the eyes and so facilitate scholastic progress, especially when Johnny sees apparently as well without the glasses as with them.

Should not an eye health program aim to prevent symptoms rather than await them? If the hyperopia is facultative, shall the child be ignored until the hyperopia becomes abso-

lute and can be detected with the Snellen test? If the administrators of the screening program fear over-referrals, will the teacher be less timid with her judgment? According to Scobee, teacher judgment under favorable conditions proved highly unreliable. Fortunately the child is frequently wiser than his elders, and his insistent complaints finally secure parental attention, independent of the screening program.

How can an ophthalmologist tell how well a screening program works unless he actively participates in some way? It is conceded that in children under nine years both the test for near vision and the screening for hyperopia often give equivocal results. Scrapping these tests is not the answer. Rather the challenge should be to improve them further so as to attain a higher percentage of correct referrals. The practicing ophthalmologist should understand the problems of visual screening. If he tactfully handles a case of over-referral, the parent will be happy to have the authoritative assurance that the child's eyes are normal and will consider the examination very worth while.

DR. EDWARD ZEISS reviewed the school vision screening program for the State of Wisconsin. An outline of this program follows:

A. Planning Committee, to include:

1. Public Health Nurse
2. School Personnel
 - a. Superintendent or Principal
 - b. Teachers
3. Parent Representatives
 - a. Health Council
 - b. Parent Teachers Association
4. Medical Personnel
 - a. Ophthalmologists (in an advisory capacity)
 - b. Health Officer
5. Other interested persons

B. Development:

1. Selection of the vision test to be used.
It is emphasized that no specific test is foolproof. The test chosen depends upon the *intelligent administration and interpretation of the result.*
 - a. Snellen test charts equipped with some means of standard illumination (time tried means of testing visual acuity).
 - b. Other acceptable mechanical devices for screening purposes may be used by ade-

quately trained personnel. The results of these tests should be realistically evaluated.

- c. Massachusetts Vision Test
- d. American Optical Co. Sightscreener
- e. Keystone Telebinocular
- f. Bausch & Lomb Orthorater

2. We suggest that in all screening procedures a pair of +2.00 spherical lenses be placed before both eyes to reveal high degrees of hyperopia.
3. The value of tests for heterophoria and stereopsis, as applied to school vision screening programs, is doubtful.
4. Grades to be screened:

It is suggested that Grades 1, 4 and 7 be screened annually. The Vision Program can conveniently be synchronized with the Audiometric Screening Program.

C. Administration:

1. Public Health Nurse recommended to be director of program.
2. Volunteer lay women, trained by medical committee and/or public health nurse under the direction of the Medical Committee, to administer initial vision screening tests.
3. Public Health nurse to recheck children who fail initial tests.
4. All children having unsatisfactory vision tests as well as those having visible lid, muscle or other ocular defects should be referred for further eye examination and refraction.
 - a. Form letter to parents of the child with a visual defect, advising further examination by an eye doctor.
 - b. Form to include space for the examining doctor to record his recommendations; to be returned to the Planning Committee by the doctor.
5. Follow-up letters and visits by public health nurse if referral recommendation is ignored.
6. Liaison between public health nurse and classroom teacher.

D. Employment of special funds to facilitate program:

1. Service clubs and private organizations to be interested.
2. Uses of such funds:
 - a. Purchase of screening test equipment.
 - b. Clerical, stationery and mailing costs.
 - c. Financial aid for professional fees and glasses in needy cases.

DR. SAMUEL SCHALL: I would like to bring up, for your information, that there is a serious shortage of trained personnel in the Chicago school system for doing visual testing. The system in the past has trained mostly teachers who do the testing and do

this exclusively. They are now being eliminated in this work due to the shortage of teachers and it is now becoming dependent upon lay personnel—P.T.A. people who will do this.

A visual screening program as Dr. Lawson mentioned, is ideal each year for each child, but it is an impossibility in the Chicago public school system. At best, they try and do it in the first and sixth grades.

I think it is commendable that we, as ophthalmologists, are starting to look into this problem because, in the city of Chicago, this has been something that the optometrists have gone after. They are doing a fairly good job, getting a large number of referrals which is a different story than Dr. Zeiss just mentioned. As a matter of fact, in a study that I have just completed for the Board of Education in Chicago, we found that a great number of the normal people who were referred, as well as the people who are visually handicapped, the partially sighted and blind children, are being referred to a large extent to optometrists. Recent surveys show that at least a fourth of partially sighted children who have visual defects are now being seen annually by optometrists. It was a pleasure to hear the speaker and the discussions. I am very delighted that the ophthalmologists are taking a hand in this, and it should go further.

DR. LAWSON: I would like to thank Dr. Lebensohn for his didactic discussion of what should constitute a screening program. I do feel, however, that when it comes down to being called upon to supervise a school system,—what should be done, what you can do and what is practical, you must be equipped with the facts and figures and with what is available.

It would be ideal for an ophthalmologist to see all the children, since this is the only way you are going to find all abnormalities. But when you are the superintendent of schools or the nurse, and you get a high rate of over-referrals, the whole program can fall apart. Our program is not perfect by

any means, but I do think that more and more we are going to be called on to answer these problems, and we must know something about what each system has—for or against it.

As Dr. Schall has discussed, personnel is important and when it comes to using a binocular instrument, it is difficult to obtain trained personnel. If trained personnel is not available, the Snellen test is probably the most simple type of test to give. I would like to mention that the National Foundation for Eye Care is studying this problem and probably within the next year, they will come out with a study of their own. I am very happy to hear from Dr. Zeiss on his experience in Wisconsin. I think this is an important problem, and we can't learn too much about it, and I appreciate the privilege of appearing here tonight.

DETAILS OF THE TECHNIQUE OF CYCLODIALYSIS

DR. KARL ASCHER of Cincinnati discussed the operation of cyclodialysis for open-angle glaucoma and presented the details of his technique. First of all he felt that the operation should be performed on the upper half of the eyeball so that if there is bleeding it will not collect and organize in the cleft. Secondly, the sclera should be incised at an angle of 45 degrees to facilitate entrance of the spatula. The sclera should be grasped between the incision and the limbus with a fine-toothed forceps, and after introduction of the spatula the two instruments are brought toward each other. As soon as the spatula enters the anterior chamber it is withdrawn and further thrusts in a radial direction are made nasal and temporal to the original one. This prevents piercing of the iris and injury to Descemet's membrane.

Discussion. DR. PETER KRONFELD: It will please Dr. Ascher to hear that a method very similar to his, a multiple-thrust method, was developed at the Illinois Eye and Ear Infirmary in Chicago in the days of the very high incidence of glaucoma secondary to de-

layed chamber formation after cataract operation.

The multiple-thrust technique has superseded the classical technique of Elschnig. The reason for it is that gonioscopic postoperative examinations quite clearly showed that the multiple-thrust technique produced a cleaner and less traumatic separation of ciliary body and iris from the anterior angular wall. This was particularly true for the cases with extensive peripheral anterior synechias. There, the obstacle that the spatula has to overcome is of much greater magnitude than in an eye with primary glaucoma. I recently reviewed our cyclodialysis cases and that review convinced me that the multiple-thrust method gave better results than the original Heine technique.

With regard to the chamber angle configuration, the pre-existing chamber angle configuration most conducive to a permanent supraciliary cleft, I used to think just as Dr. Ascher does, that a very narrow entrance to the angle augurs unfavorably. Just recently Dr. Chandler of Boston convinced me that that is not 100 percent true. Dr. Chandler has a sizable series of cases of what he calls neglected angle-closure glaucoma. That is angle-closure glaucoma in which the angle is completely closed, in which the diagnosis was not made promptly or the treatment was not instituted promptly. At any rate, you are dealing with an eye with very high pressure and a completely closed angle. And in these cases, Dr. Chandler has obtained satisfactory results with his combination of iridectomy and cyclodialysis: not only normalization of the intraocular pressure but even subnormal intraocular pressure which is so characteristic of some cyclodialysis operations.

The finding of Dr. Ascher's that cyclodialysis in the upper quadrants has a better chance than cyclodialysis in the lower quadrants is very definitely brought out by our series at the Infirmary. The cyclodialysis operation has a very definite place in my armamentarium, but—I don't believe that I would describe the operation as safe without quali-

fying that term "safe." I would want to qualify that word "safe" because the complications of cyclodialysis operations, and I mean complications—I don't mean improper technique, are what I would call distinctly nasty. I would call them serious and they certainly lead to irreparable damage. I am thinking here primarily of cases in which permanent corneal edema developed in eyes in which I could very clearly see that the actual contact between the spatula and the corneal epithelium was minimum. It is true that both of those two cases I am thinking of now were reoperations, and it was in the second operation, which I think was done according to all the laws of the textbook, that permanent corneal edema set in. Just as serious is the perforation of pars plana with severe vitreous hemorrhage which I have also seen in eyes in which I have thought the technique was proper. What concerns me most about the cyclodialysis operation is that I have the feeling that I control the outcome of the operation to a very much lesser degree than I control the outcome of an iridencleisis or a sclerectomy, and it is that feeling of helplessness as to the outcome of the operation that makes me feel so uneasy.

But, aside from all that, this has been a very pleasant presentation, and we are all very much indebted to Dr. Ascher. I have enjoyed particularly his bringing to our attention again some of the great ophthalmologists of the old world.

DR. JOSEPH S. HASS: I have enjoyed very much Dr. Ascher's paper, and I certainly subscribe to the theory that the multiple-thrust technique is far and away the least traumatic in the techniques of cyclodialysis. I think all of us who do them presumably have idiosyncrasies and I have my share.

I think from the technique standpoint, that the use of a 4-0 black suture in lieu of Dr. Ascher's fixation forceps is a very much more secure way to hold the sclera and works very satisfactorily. This is placed instead of the forceps and is used for the fixation.

I should like also to mention that I believe there is one indication for doing a cyclodialysis in an inferior quadrant. Dr. Ascher has pointed out that cyclodialysis works well as a secondary operation, especially well after iridencleisis, and I feel that the traction exerted by the incarceration of the pillars may be utilized to advantage in maintaining an open cyclodialysis, but if one is to utilize traction of the incarcerated pillars, then in this instance, the cyclodialysis cleft should be made in an inferior quadrant.

There is one point too I should like to emphasize from a standpoint of technique. This has not been mentioned tonight but during my training and in many institutions that I have visited, people have advocated the insertion of air following cyclodialysis to control hemorrhage. In my experience, this is something that has worked more deleteriously than advantageously. This is especially true to phakic rather than aphakic eyes. If one is attempting to make a cleft between the sclera and the ciliary body, and then one forces a considerable amount of air into the anterior chamber to push back on the iris-lens diaphragm, this pressure will take effect in the vitreous body and will then be exerted equally in all directions throughout the posterior portion of the eye. There will be pressure exerted against the ciliary body which will tend to close rather than open the cleft. I think it much more preferable, if you wish to form the anterior chamber following the cyclodialysis, to use saline which will be able to diffuse into the cleft behind the iris and be more equally distributed and thus offer much less pressure against the ciliary body.

I think that is enough about technique. I was trained to make my incision over the pars plana and I have since modified that to bring it forward because the incidence of staphyloma following unsuccessful cyclodialysis, when your incision has been made too far back, is a real one. Therefore, I think it is much safer to make the scleral incision over the ciliary body where there is more support for the uveal tissue.

Now Dr. Ascher reported that O'Brien, Weih, Stein and Elschning succeeded in 79 percent of their cyclodialyses. This is an excellent percentage of success in glaucoma. It is somewhat confusing that Sugar reported 52 percent successes, between one to five years, which dropped off later to 46 percent at the end of five years. McPherson from the Wilmer Institute reported only 42 percent success. Assuming though that the percentage of success is up close to 75 percent, this is near the filtering operations, or perhaps even better than the filtering operations, then the advantages of cyclodialysis operation would be tremendous—the cosmetic advantage, the ability to repeat cyclodialysis and the lack of late infection. All of these are real advantages. There must then be some reason why cyclodialysis is not more universally done and Dr. Kronfeld has more ably than I pointed out some of them. I should like to add my share of the disadvantages of cyclodialysis to this discussion.

I think the one that perplexes me the greatest is hypotony. For I find that in a high percentage of the cases in which I do cyclodialysis, hypotony occurs and all the attendant complications of hypotony then ensue. It is not unusual to see macular edema with a loss of central acuity in the hypotony of cyclodialysis. It is not unusual to see a slow-forming cataract which occurs very commonly in the hypotony of cyclodialysis.

And then there is one other complication which I should like to emphasize and that is sudden closure of the cleft. Those of you who do very many of these and are aroused at 3:00 A.M. by a person with extremely painful acute glaucoma will be familiar with the complication of sudden closure of the cleft. To bore you for a few minutes, I should like to mention one case of a woman from Wisconsin on whom I had done an iridencleisis which failed and then a successful cyclodialysis. Three years after the operation this patient called me one day and said she was in excruciating pain. I had watched this woman very carefully and her

tension had been 45 mm. Hg before the cyclodialysis was done. Following the cyclodialysis, the tension was soft, a cataract formed in a year but the eye was still secure. She called me, said she was in excruciating pain, what should she do about it. I knew what had happened and suggested that she come to Chicago on the next train. She called me the next day and said she was comfortable and I suggested she still come. When she arrived here, the most astounding thing had happened. This woman's tension was then 22 mm. Hg, she had a filtering bleb over her iridencleisis and the cyclodialysis cleft was closed, which emphasizes the force of late closure of a cyclodialysis because these things close up with a bang and the tension goes sky high. In this case, it was enough to open up a three-year-old iridencleisis.

Now, aside from the disadvantages, I agree with Dr. Ascher and Dr. Kronfeld that cyclodialysis has a very definite place in the field of glaucoma surgery. I think that it is the primary operation for glaucoma secondary to peripheral anterior synechias following cataract extraction and in delayed reformation of the anterior chamber.

It is so advantageous because the flap is scarred down, you can't do a filtering operation well and the danger of vitreous prolapse is present. I think it is also a great advantage as a secondary operation following failure of a filtering operation, either one or two. For here again, you have no more room for a filtering operation and cyclodialysis provides a fine mechanical way of lowering the pressure when it succeeds.

Finally, I should like to correct a misimpression I may have given in the past that cyclodialysis was effective in infantile glaucoma. Someone asked me about that a few days back. I did not ever mean to give that impression for I have never seen a successful cyclodialysis in infantile glaucoma.

I again thank Dr. Ascher and Dr. Kronfeld for allowing me to follow them in this discussion.

DR. K. W. ASCHER (closing): I was sure

that when I came to Chicago I would go home having learned quite a bit, and I thank the discussers very kindly.

I would say to Dr. Kronfeld's remarks about Chandler's research, if I am properly informed, he always added the iridectomy to these procedures when he had to attack a closed-angle case. This, in itself, speaks in favor of the remark that I made that surgeons, dissatisfied with the cyclodialysis, try to improve it by adding this or that procedure to make it more efficient. I do think that the cyclodialysis in itself, as described tonight, would not be very recommendable in narrow-angle glaucoma whether recent or neglected because of the fact that there is a very definite tendency in these cases to reform the synechia even with all effort being made to keep it open.

About permanent edema of the cornea, this is extremely interesting. I do know that it has been described, and I just wonder whether these cases might have been predisposed to that, due to some pre-existing condition in the cornea and in the same way as we examine every case diligently under the corneal microscope before doing cataract surgery, I think we also should do a similar procedure before glaucoma operation. We might avoid cases with endothelial-epithelial dystrophy which may be aggravated by surgery.

If the instruments are properly shaped and the procedure is performed in the way it is described, it is difficult to understand why, in these cases, deleterious corneal edema should develop since we do not touch any of the structures which may produce this corneal edema. But, of course, the experience of surgeons like Kronfeld speaks for this possibility.

To Dr. Haas's remarks, I wanted to confess that I did not mention the bridle suture which I always use. In addition to this bridle suture in the superior rectus muscle tendon, which I use in every intraocular operation, I use forceps because of the fact that I feel that it is bringing spatula and pectinate liga-

ment together in a way which cannot be handled as easily with the bridle suture. You cannot, in my opinion, bring the spatula against the pectinate ligament without having two real fixed points. It must be a metal instrument and cannot, in my opinion, be supplemented by sutures. I may be wrong.

Very good is the idea of the inferior quadrant in cases where there is some pull from above. I like that very much. It is new to me, and I am grateful for this suggestion.

About the introduction of air. I make a little remark which is not meant to be nasty but if you inject saline in the same amount, I mean cubic mm, you get, at least for a moment, the same amount of pressure. Saline you say is being absorbed which is right, but the air, the oxygen at least, disappears pretty soon from the anterior chamber. Not as soon as the saline, I agree with you in that. I think this is a good point, and it was most interesting to me.

In 1951, Kirby mentioned precautions about the injection of air into the anterior chamber, saying that we must be very careful not to inject too much.

The percentages of success—I should have mentioned and am glad to mention it now, that the series in Prague as well as in Budapest are patients of the charity clinics. In a city of the size of Prague or Budapest, this is fluctuating material. People do not come back for 10 years. They do not often lend themselves to observation for long periods of time. I do not offhand recall the time limit. I do know that most of the cases by Stein were observed for some six months or one year or something like that. From my own private patients, I do recall that quite a few maintained very good pressure and had good eyesight for many, many years. I won't go into figures because I don't have them at hand. It is very possible that of these original good successes in Prague and Budapest some deduction has to be made as time goes on. One thing is interesting about hypotony. I did not see any in our material and I do not recall that we had definite hypotony after

cyclodialysis, if performed in this conscientious way. I know of hypotony after trephine operations, but I do not think that it is as common after cyclodialysis as it is after trephine operations. I may be wrong but this is my definite impression.

I thank you very much for your patience and for your very valuable advice.

David Shoch,
Recording Secretary.

NEW ENGLAND
OPHTHALMOLOGICAL
SOCIETY

445th Meeting, December 17, 1958

DR. HENRY L. BIRGE, *presiding*

FORUM ON PSYCHIATRY IN OPHTHALMOLOGY

MODERATOR: HENRY L. BIRGE, M.D. DIS-
CUSSORS: FRANCIS J. BRACELAND,
M.D., ALFRED KANT, M.D., AND
DAVID STONECYPHER, M.D.

What is the outlook for children with hysterical amblyopia of one or two years' duration? Does the same apply to young adults?

DR. BRACELAND: If the hysterical amblyopia has lasted one to two years that is a little bit longer than we like to see it. It is well to remember that children react very frequently in a hysterical fashion. It is well to remember also that they are pliable, they haven't settled down, and these hysterical states are not nearly as serious as they would be if they occurred in later life.

Hysteria is a very primitive form of reaction, the most primitive, yet it can be seen among the high placed. I saw it in some people during the war who were directing things including, if you please, a most important man who had real gun barrel vision.

Now in a child I would say the outlook is very good. A child will respond well. A child will believe you. He is much more ready than an adult to believe that emotional things can cause symptoms and he is

twice as ready as the average doctor to believe that emotional things can cause some of the symptoms he has.

As the individual gets older the condition becomes seemingly more malignant. Perhaps because hysteria is such a primitive reaction. Here it is more difficult to gain the patient's co-operation and more difficult to effect a cure or gain some relief.

Should restraints be used in postoperative cataracts patients, one eye patched, who have become disoriented?

DR. BRACELAND: I would think, if it is possible, the use of some of the present-day medications would be much better than the use of restraints. When restraints are put on a disoriented person, one in a delirium, they become convinced that you and the others of the group are going to hurt them. The patient feels he must struggle all the more in order to save his life. Here is the danger.

However, in some cases, it may be absolutely necessary to use momentary restraints until sizable doses of the drugs can be administered to put the patient asleep.

Should a patient seeking glasses or drops and showing no physical need for the same be given a placebo and encouragement, or encouragement and reassurance alone.

DR. BRACELAND: I think this depends in most cases on the intelligence of the patient. Be honest with the patient, don't have him feel that you are rejecting him. Tell the patient that at the present time you see no reason for giving him glasses. Suggest strongly that he come back in one or two months. This way you do not abandon the patient, you do not reject him. So many of these people fear rejection by the doctor who appears to be too busy to talk to them, who appears to have too many patients to care for them properly. Tell them to come back at another time and you will have another look at them. Do it in a complimentary fashion, leave the door always open, as it were, for them.

What are your feelings regarding the use of hypnosis by nonpsychiatrists?

DR. BRACELAND: It depends on who the nonpsychiatrist is. I would approve of hypnosis by any doctor who learns it. The doctor must realize what the difficulties are, what he is liable to get into, and he must take the proper precautions. One precaution is always have a third party in the room particularly if the subject is a lady. While under hypnosis ladies have been known to get some very peculiar ideas; ideas not too different from what they get when under the influence of the gas that dentists use, as dentists have sometimes found out to their sorrow.

How do you explain the defective vision with no organic cause seen in early teenage females? What advice should be given to the parents?

DR. BRACELAND: This is another symptom of the old chlorosis which has all but disappeared as you know. In the history of our hospital two of the causes that used to be given for insanity in females were chlorosis and tight lacing.

The growing female, the teenage female, is full of all kinds of emotional difficulties. She is trying to do so many things and so many things are happening to her. Consider the physiologic changes that are occurring to her. Here she is externally a woman; internally, frequently, a child holding on to her parents and regretting it. She is fearful to take a step forward and yet wanting to do it very much.

In cases such as this where there is no organic cause I would think the proper advice to give to the parents would be to have them look elsewhere with the physician for some underlying emotional problems. But also remember to keep the door open, don't abandon or reject these patients, you can help them if you try.

When you are treating a patient with hypnosis do you allow them to remain for days or even months under the influence of the hypnosis?

DR. KANT: The patient is always brought out from his or her trance state with the suggestions of well being, euphoria, and relaxa-

tion, just in case one has made any inadvertent suggestions that one had forgotten about, then there is no difficulty. Now with regard to the more underlying question here—on the part of those people who know hypnosis and who have studied it, they say it is difficult to know how much of the effect persists and whether it persists for days or months.

Does hypnosis have the primary effect on the thalamus? Is it of benefit in vascular hypertension and intraocular hypertension?

DR. KANT: In hypnosis the patient is really enjoying his own intrapsychic environment. The effects that we get on the cortical no doubt have effects on the lower centers. But specifically, when we speak to a patient we like to feel that we are addressing ourselves directly or indirectly to the subconscious mind and if the thalamus is a part of that, which of course it is, then in part the question is answered. Those cases of intraocular hypertension which may be glaucomatous as well as hypertensive on the vascular basis are very tense individuals. In these cases we have had very good success.

Tell us of a case of glaucoma where the use of hypnosis resulted in lowering tension.

DR. KANT: One case I have in mind is that of a physician, a pathologist. This man was very tense and he had many psychiatric problems for which he would not seek help. I simply told him that he was going to enjoy being relaxed and I told him he was going to continue to stay relaxed after he came out of the trance for as long as it was good for him and his subconscious mind would tell him when to break it off. One does not say to a patient your ocular tension will now be lower; this of course would be fruitless. The problem, however, can be approached in a different way.

Have you had any experience with severe blepharospasm of the bilateral type and with unilateral seventh nerve tic?

DR. KANT: I have seen these blinkers and in some instances it seems to have helped them to use hypnosis. Hypnosis is helpful in cases of severe keratitis of an allergic basis.

A relative degree of analgesia can be suggested to these patients and they can enjoy themselves quite comfortably without the necessity of the reflex blinking. I have had two cases of unilateral seventh nerve tic. One patient was a woman who was most resistant and obviously anxious. With a patient like this, my practice of hypnosis ceases. The other patient who had this twitch which had started to radiate to the face, I gave suggestions on relaxation and after demonstrating various types of phenomenon to him he was able to let this thing go. But not before we allowed him to substitute a little bit of a twitch to his left little finger tip if he needed it. This man refused to see a psychiatrist.

PERIPHERAL IRIDECTOMY IN ANGLE-CLOSURE GLAUCOMA

DR. PEI-FEI LEE, Boston: The purpose of this study was to determine the efficacy of peripheral iridectomy in controlling intraocular pressure in eyes demonstrated to have angle-closure glaucoma and to compare the effectiveness of prophylactic peripheral iridectomy in preventing an attack of angle-closure glaucoma in an uninvolved eye whose fellow received a therapeutic peripheral iridectomy for angle-closure glaucoma.

In 59 patients selected, 74 eyes demonstrated primary angle-closure glaucoma and received therapeutic peripheral iridectomy. Thirteen fellow eyes with no demonstrated pressure elevation and no disc or field change, but with gonioscopic findings indicating susceptibility to angle-closure glaucoma were

given prophylactic peripheral iridectomy. The technique used was that described by Chandler (*Arch. Ophth.*, 47:695, 1952). None of the eyes were gonioscoped on the operating table. A combined procedure of peripheral iridectomy with "angle-sweeping" or anterior cyclodialysis was performed in some eyes with demonstrable peripheral anterior synechias.

Results of this series show that there has been no recurrence of acute attacks after therapeutic peripheral iridectomy in 74 eyes, and no attack has occurred after prophylactic peripheral iridectomy, in the 13 eyes. This investigation supports the concept that peripheral iridectomy is more effective than miotics in preventing an attack in the second eye.

Peripheral iridectomy is highly effective in the treatment of properly selected cases of angle-closure glaucoma. In this series peripheral iridectomy alone was, without exception, effective in preventing further attacks of angle-closure glaucoma. This operation was very effective in normalizing tension and in preventing further damage to disc and field when carried out on an eye which had shown little or no damage preoperatively.

In eyes with glaucomatous pallor, or cupping, with significant field defect, peripheral iridectomy alone is contraindicated, because even if intensive medical therapy is used after iridectomy further damage will probably not be prevented.

Charles Synder,
Recorder.

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VITH CONGRESS OF THE PAN-AMERICAN ASSOCIATION OF OPHTHALMOLOGY

The Vith congress was held at Club Puerto Azul, Naiguata, Venezuela, on January 31st to February 7th. Naiguata is approximately 16 miles south of La Guaria, the port of Caracas, which is 13 miles farther north. The club is beautifully situated on

the Caribbean Sea and consists of a number of ultramodern buildings, giving adequate facilities for all the accommodations that were required. There are two fine beaches, one of which is protected and quiet, the other on the sea with active and sturdy "rollers." The temperature of the water was about 70° F., and the weather was perfect. There are also swimming pools, tennis courts,

bowling alleys and a golf course nearby. No effort was spared to make the guests happy and comfortable.

The congress was originally planned to be held in Caracas, but hotel facilities were scattered and other difficulties of transport, traffic, and so forth, created many problems. The local committee of organization, therefore, wisely and most happily changed the plans. It was a great convenience to all of the delegates to hold the meetings and most of the social activities under one roof, so to speak.

The executive president of the VIth congress was Prof. Dr. Jesús Rhode of Caracas, who presided with skill and charm. The president of the association was Dr. Brittain F. Payne of New York, who completed his arduous four years of office, most ably and graciously, on the termination of this congress. The congress was brilliant and most successful and the executive president and his committee on organization deserve the utmost commendation and gratitude on the part of all of those who were privileged to attend.

The inaugural session was held in Caracas on the morning of January 31st in the beautiful auditorium of the Aula Magna, of the Ciudad Universitaria. Following the Venezuelan national hymn by the Central University chorus of young men and women, the invocation was given by Bishop José Rincón Bonilla. The Minister of Public Health and Social Assistance, Dr. Arnoldo Gabaldón, representing the President of the Republic, officially opened the congress. Prof. Rhode gave an eloquent address of welcome. Then followed a response for the members by Dr. Hilton Rocha of Brazil, vice Dr. Werther Duque Estrada whose plane had been delayed. Dr. Rocha gave a fluent extemporaneous address in which he paid homage to the memory of Moacyr Alvaro, the recently deceased secretary-general of the association. Dr. Brittain F. Payne, president of the association, continued the session with his address in which

he praised the work and contributions to ophthalmology by the Latin Americans, the hemispheric work for the prevention of blindness fostered by our colleagues in the association, and for the work of Prof. Rhode and Prof. José Manuel Espino, the honorary president of the congress and the members of the organizing committee for their outstanding efforts to ensure success of the congress. He acclaimed the great Liberator of South America and Venezuela, Simón Bolívar and paid tribute to great founder ophthalmologists of Venezuela, Dr. José María Vargas (1786-1854) and Dr. Eliseo Acosta (1819-1879).

The first part of the session concluded with a number of native songs by the university chorus of exquisitely trained voices. One of the songs, a sort of Negro-Indian spiritual called "Mampulorio" was especially thrilling, with its piercing lament.

Following a short intermission, the morning's program concluded with a moving eulogy of Moacyr E. Alvaro by Dr. Santiago Barrenchea of Chile. Next came the Harry S. Gradle Lecture which was given by Dr. Ivo Correa Meyer of Brazil, who spoke on diseases of the macula. The first Gradle Medal for outstanding teaching in the field of Pan-American ophthalmology was presented to Dr. Brittain F. Payne by Dr. J. Wesley McKinney on behalf of the association. The session closed with the singing of the lovely university hymn by the chorus and a floral offering at the National Pantheon in the name of the association to the Liberator.

The members of the congress were then taken by bus to the station of Teleférico del Avila and ascended another 3,000 feet to the striking cylindrical and modernistic Hotel Humboldt, where they were lavishly entertained at a buffet lunch of native dishes by the Governor of the Federal District, Carrillo Batalla, and his lady. The views from the hotel of the city on one side and the Caribbean Sea on the other side are unforgettable.

The tired, replete and happy members of

the association were then returned to Puerta Azul by bus where they all safely arrived an hour and a half later.

The scientific sessions began the next morning and were held daily throughout the week. One of the two halls used for this purpose had facilities for simultaneous translations, which were admirably done but at a great cost to the local committee. The scientific program consisted of 138 papers, a number of which were not given, however, because of absence of some of the contributors. The invited guests-of-honor were Dr. Rudolf Thiel of Western Germany, who spoke on "An attempted synopsis of the physiology and pathology of the systemic and ocular vascular system"; Dr. Horacio Ferrer of Cuba, who was unable to be present; Dr. Frederick C. Cordes of San Francisco, U.S.A., who spoke on "Retinal detachment following congenital cataract surgery"; Dr. Derrick Vail, Chicago, U.S.A., who spoke on "Modifications of the surgery of cataract by the use of alpha chymotrypsin"; Dr. Alan C. Woods of Baltimore, U.S.A., who gave us "Modern concepts of the etiology of uveitis"; and Prof. E. Velter of France, whose death in September, 1959, was a severe blow to world ophthalmology. Special guests were Dr. Esme V. Anderson of Melbourne, Australia, who spoke on "Flying doctors"; Dr. H. Arruga of Barcelona, Spain, who gave us his experiences with the use of his girdling suture in 120 cases of retinal detachment; and our peripatetic friend, Dr. Ida Mann of Nedlands, West Australia, who spoke on "Regional ophthalmology: Its problems and its value as a study."

Symposia were held on space ophthalmology, ocular manifestations of hereditary syndromes of head and neck, recent advances in the management of glaucoma, experiences with enzymatic zonulolysis (appropriately led off by Joaquín Barraquer of Barcelona, Spain), detachment of the retina, prevention of blindness, vertically incomitant horizontal strabismus, recent progress of

ophthalmic therapeutics, recent advances in ocular surgery, surgery of cataract, regional ophthalmology, glaucoma and strabismus. There were a number of excellent "free" papers. Twenty-four scientific films were shown, 10 of these by our Latin American colleagues.

There were very good scientific exhibits held adjacent to the meeting halls. Of these, the first award was to C. D. Dukes, H. H. Fox and L. J. Girard of Baylor University College of Medicine, for their exhibit "Time lapse cinematography of ocular tissues with interference microscopy." The second award went to Dan M. Gordon of Cornell University Medical College for his exhibit "Inflammations of the eye." And the third award to Alberto Rivero of the Institute Oncologia Luis Razetti of Caracas, for his exhibit of excellent colored clinical photographs.

Nearby was a small but interesting commercial exhibit which included the ubiquitous Coca-Cola and Pepsi-Cola stands, presided over by pretty but modestly dressed Venezuelan girls.

The wonderful, planned social events included magnificent cocktail parties by Dr. and Mrs. Jesús Rhode, Dr. Ignacio Luis Arcayo, Minister of Foreign Relations, at Casa Amarilla in Caracas, and his excellency the Ambassador of the United States and Mrs. Edward J. Sparks in the beautiful embassy building. The members were also entertained by an evening of colorful folk dances, a barbecue and dance to native music on the beach under the "swaying palms," and a beautiful concert by the Venezuelan orchestra in the Municipal Theatre, Caracas.

A severe blow to the congress occurred just prior to the official banquet on February 5th when the honorary president of the congress, Dr. José Manuel Espino suddenly collapsed and died of coronary occlusion while getting out of his car. Dr. Espino was one of the most revered and beloved members of the association and his dramatic and sad end cast a heavy depression on all

of us. Tribute to his memory with an orchid at his empty place at the table of honor was reverently paid. The banquet proceeded but there was no music or dancing or speeches and after dinner the members sadly disbanded.

The closing ceremony was held on the morning of February 6th with the presentation of the medal of the National Society for the Prevention of Blindness to Dr. Conrad Berens by Dr. John Feree, the executive director of the N.S.P.B. Then followed a short eulogy to the memory of Dr. Espino, and short closing addresses by Drs. Payne, Rhode, and the new president of the association, Jorge Valdeavellano of Lima, Peru.

In the afternoon, the remaining members of the congress were entertained to lunch and a viewing of the horse racing by the director of the Instituto Nacional de Hipódromos, at the new and very beautiful Rinconada Race Track. The eighth race of the day was dedicated to the VIth congress. It was won by a horse named Lo Adopto, who paid well. A cup was presented the winning owner by the association. The following officers of the association for the next four years were elected:

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 Dr. Derrick Vail

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Dr. Benjamin Boyd, Panama

The next congress, the VIIth, will be held in Montreal, Canada, October 4-10, 1964. Interim congresses will be held in Lima, Peru, in 1961; Caribbean area in 1962, and some place in the United States in 1963.

The total registration was a little less than five hundred, about evenly divided between the two continents of the Western Hemisphere.

The long-awaited Directory of the Association made its appearance. It was published by the Liaison Committee, the chairman of which is Mr. W. C. Conner, president of the Alcon Laboratories, Inc., of Fort Worth, Texas. It is a job well done and will be most useful for all members of the association. The committee deserves our sincere thanks for this tool.

It is my opinion that this congress is one of the best for scientific contributions and extracurricular glamor yet held. Those of us who were unable to attend have missed an exhilarating experience, marred only by the sudden death of Dr. Espino on the eve of the closing of the congress, an end that would have pleased him.

Derrick Vail.

CORRESPONDENCE

OSMOTIC PRESSURE MEASUREMENTS

Editor,
 American Journal of Ophthalmology:

I should like to humbly point out that in the experiments by Kass and Green on "Osmotic pressure measurements of intraocular fluids by an improved cryoscopic method: Physiologic significance relative to aqueous humor dynamics" (Am. J. Ophth., 48: 32 [July, Pt. II] 1959), two factors have been neglected, or at least the reader was not informed of their introduction. The

failure to introduce these factors invalidates the scientific significance of the experiments.

The first factor, and the one with which ophthalmologists are more familiar, is the temporal sequence of the eye chambers' tapping. We know that any escape of intraocular fluid is replaced by "secondary" or "plasmoid" aqueous. This has mainly a higher protein concentration than normal aqueous, and is naturally osmotically more effective. In the above experiments the anterior chamber was tapped after the posterior chamber. Naturally then the fluid obtained was osmotically more effective.

The second factor concerns the physicochemical properties of the solutes in the aqueous. Since freezing-point reduction depends on these solutes, we first have to know what they are.

The eye's form and tension is kept by the intraocular pressure. In contrast to the blood pressure this is not maintained by a mechanical pump like the heart but is an osmotic pressure! Osmotic pressure is created by osmotically effective solutes.

The globe's contents consist chiefly of the vitreous body and to a lesser degree of aqueous. Vitreous in turn consists mainly of mucopolysaccharides* (or as now termed: glycosaminoglycans). Their concentration in aqueous is quite high, too.

Glycosaminoglycans have a tremendous capacity to attract water! Chemical and physical properties of these substances have not yet been fully investigated; we do not even know exactly what they are. The mode by which they attract water can only be guessed.

The reduction of the freezing point of water by solutes depends on their dissociation into electrically charged ions and on the bipolar nature of the water molecule, not alone on the solutes' concentration.

Since the osmotic effective substances in the eye are glycosaminoglycans (mucopolysaccharides), we first have to know them and their properties. This information we

unfortunately do not yet possess and cannot, therefore, draw conclusions from a physical measurement that depends on so many unknowns!

(Signed) Harri H. Markiewitz,
Brookline, Massachusetts.

* * *

Editor,

American Journal of Ophthalmology:

Please accept my apology for returning to the same subject; I feel though that the importance of the matter warrants further discussion.

In the above paper it is stated (p. 42) that "The freezing-point depression and osmotic pressure of a solution are colligative properties, dependent only upon the number of dissolved particles, regardless of the nature of such."

I think it a grave error to apply this statement to the aqueous humor. Colligative properties apply only to solutions of nonvolatile solutes and are usually used in binary ideal solutions.

In the above form the statement denies the dissociation of solutes into electrically charged ions (Arrhenius, 1887), the bipolar nature of the water molecule and the ionization of water. Not to mention the ionic strength and Debye-Hückel theory (1923).

Furthermore, the aqueous humor is not only a solution of crystalloids but a lyophilic colloidal solution, too, in which proteins, glycosaminoglycans, and other intrinsic colloids are present.

In solutions of colloidal electrolytes it is necessary to distinguish between the total osmotic pressure and colloid osmotic pressure. It is furthermore necessary to take physical adsorption and chemisorption into consideration. Colloid chemistry is a science by itself, with its own rules and complicated formulations.

In the eye we do deal with lyophilic intrinsic colloids, like proteins and polysaccharides. Colloid-chemical laws must then be taken into consideration. Electronically com-

* Balazs, E. A., Retina Foundation, 30 Chambers Street, Boston 14, Massachusetts.

puting the electrolytes' concentration in this colloidal system is, in my humble opinion, insignificant as long as the nature of the colloids and the semipermeable membranes is unknown.

To schematically illustrate my point, Figure 1 is enclosed.

That the total osmotic pressure in the posterior chamber is higher than in the anterior one can easily be inferred from the situation in iris bombé. There the semipermeable iris completely separates the chambers. Since the iris bulges into the anterior chamber, the osmotic pressure in the posterior one must be higher.

Again, I regret having to disagree with the presently prevalent thinking in the field. I feel, however, that if we are ever to solve the problem of water dynamics in the eye, we must obey the rules; these are dictated mainly by the colloids.

(Signed) Harri H. Markiewitz,
Brookline, Massachusetts.

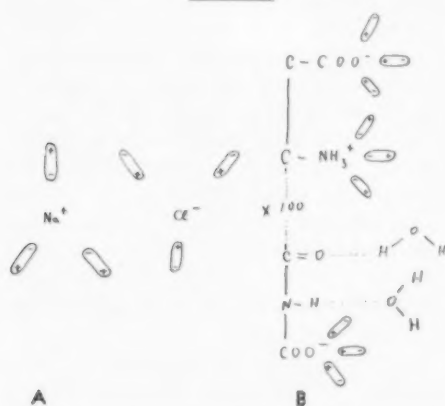


Fig. 1 (Markiewitz). (A) One salt molecule binds six water molecules, (B) the colloid molecule, several hundreds.

DR. GREEN'S REPLY

Editor,
American Journal of Ophthalmology:

I am sorry to have taken so long in writing you with regard to Dr. Markiewitz's letters of December 17 and 19, 1959, in which

he criticized the recent publication by Dr. Kass and myself (*Am. J. Ophth.*, 48:32 [July, Pt. II] 1959).

Dr. Markiewitz's contention that the aqueous humor removed from the anterior chamber of the rabbit eye *less than 60 seconds* after paracentesis of the posterior chamber represents "plasmoid" or "secondary" aqueous humor is completely unsupported by the observations and results of all investigators who have studied the chemistry of the aqueous humors. Indeed, whether you tap the anterior chamber alone or immediately after a paracentesis of the posterior chamber, the chemistry and the osmotic pressure of the aqueous humor are unchanged.

I gather from Dr. Markiewitz's comments that he would have us believe that the plasma, because of its high protein content, has a higher osmotic pressure than the aqueous humor, since he states, "This (the plasmoid aqueous humor) has mainly a higher protein concentration than normal aqueous, and is naturally osmotically more effective."

The osmotic pressure of normal aqueous humor of the anterior chamber of the rabbit eye is indeed higher than that of plasma, so that the osmotic pressure of "plasmoid" aqueous would be expected to be *lower* than that of normal aqueous humor.

Dr. Markiewitz seems to have lost sight of the fact that osmotic pressure is a physical chemical property of a solution and does not indicate the chemical composition of the solution. It merely compares the total osmotically active dissolved substances of two solutions. Therefore, contrary to Dr. Markiewitz's statement that we have ignored the contribution of the individual components of the aqueous humor to the osmotic pressure of that fluid, it is obvious that the higher osmotic pressure of the aqueous humor of the anterior chamber means that this fluid contains more osmotically active dissolved particles than does plasma or the posterior chamber fluid.

Finally, Dr. Markiewitz has confused osmotic pressure with the unidirectional

flow of fluid from the posterior chamber into the anterior chamber, when he describes the origin of the condition of iris bombé as, "Since the iris bulges into the anterior chamber, the osmotic pressure in the posterior one must be higher."

Dr. Markiewitz's sincere desire to arrive at a better understanding of the complex dynamics of aqueous humor formation is certainly to be encouraged. I sincerely trust that the foregoing comments will help clarify some of the misunderstanding and confusion reflected in his two letters.

(Signed) Harry Green, Ph.D.,
Philadelphia, Pennsylvania.

CORRECTION

Editor,
American Journal of Ophthalmology:

I would appreciate your making a note in *THE JOURNAL* about our article entitled, "Dacryocystorhinostomy with wire fistulization," which appeared in the December, 1959, issue. Please note that Figures 8 and 9 are mislabeled. The subtitles for Figures 8 and 9 are correct; however, the photographs should be in reverse order.

(Signed) Ira A. Abrahamson, Jr.
Cincinnati, Ohio.

OPHTHALMODYNAMOMETRY

Editor,
American Journal of Ophthalmology:

In the April, 1959, issue of *THE AMERICAN JOURNAL OF OPHTHALMOLOGY*, Dr. Harold F. Spalter publishes a very interesting paper entitled "Ophthalmodynamometry and carotid thrombosis."

For many years I have been working with Bailliart's technique and it is my firm belief, in agreement with Dr. Spalter, that the importance and practical value of this method are very great in the prevention, diagnosis, and in following the evolution of vascular cerebral diseases (XV Conc. Opth., Cairo, 1938).

In 1934 (*Arch. hispano-am. oftal.*, 34:616 [Nov.] 1934), I reported three cases of unilateral amaurosis and contralateral hemiplegia, with aphasia when the lesion was on the left side. These were in all probability the first papers published on the subject, so I was rather surprised not to see them mentioned in Dr. Spalter's very complete article.

Two of these cases were of the acute form: sudden onset and loss of consciousness. The third one had a sudden hemiplegia without stroke but the amaurosis (of the contralateral eye) did not occur until after a few days. In all three cases funduscopy revealed the typical image of retinal arterial obstruction. In the only case in which ophthalmodynamometry was carried out, the retinal arterial pressure was 0 in the left (blind) eye and 55/115 gm. H₂O in the right one.

The first patient was a 42-year-old man, syphilitic (Wassermann positive) and hypertensive (170/80-Vaquez). The second was a woman, aged 32 years, who had a congenital mitral stenosis. She had the stroke when dancing, and when she recovered consciousness two hours afterward, she was seen to have a right hemiplegia and left-eye blindness. Undoubtedly an embolism was the mechanism in this case.

The third and last case was an asystolic 48-year-old man: a sudden hemiplegia was the first symptom not accompanied by an ictus. Some days later he developed a sudden loss of vision in the contralateral eye, caused by a total obstruction of the central retinal artery.

The circumstance of finding in my three patients a total retinal artery obstruction joined to a contralateral hemiplegia caused me to call this clinical picture by the name of "Ophthalmosilvanic syndrome," a name accepted by Appelmans, et al., (*Bull. Soc. belg. ophtal.*, 99:454) some time later. I offer this as a supplement to Dr. Spalter's contribution.

(Signed) C. Espíldora-Luque,
Santiago, Chile.

BOOK REVIEWS

PHYSIOLOGY OF THE EYE: CLINICAL APPLICATION. By Francis Heed Adler, M.A., M.D., F.A.C.S. Saint Louis, C. V. Mosby Company, 1959, third edition. 780 pages, 372 illustrations, including two in color, index, references. Price: \$16.00.

The second edition of this famous and noteworthy book appeared in 1953. In the last six years there has been a flood of reports of research study in all fields of ocular physiology, some of it excellent, some of it conflicting, as the author points out, especially in the fields of aqueous humor dynamics and corneal transparency. These conflicts have created some problems of selection for the author. He has done his usual efficient work in resolving them to his own satisfaction and undoubtedly for the reader's satisfaction as well.

Most of the chapters have been rewritten, in view of up-to-date facts, for example, electromyography. The rewriting has been most skilfully done, as one has learned to expect from the author's brilliance and authority. The basic scholarship and literary research have been enormous, and we are left standing in appreciative amazement at the achievement.

All of us in ophthalmology, and those in the general field of physiology, are greatly in debt to Prof. Adler, who is the head of the Department of Ophthalmology, University of Pennsylvania School of Medicine, consulting surgeon to the Wills Eye Hospital, Philadelphia, and the sterling editor of the *A.M.A. Archives of Ophthalmology*.

There is no need to employ the hard sell here. Those who are familiar with the previous editions of this classic American work will need no prompting to obtain this edition.

Derrick Vail.

AN INVESTIGATION OF OPTICAL CORRECTIONS FOR ENABLING PATIENTS WITH LOW VISUAL ACUITY TO READ. By Jan

Karel Pameijer, M.D. Amsterdam, E. Kluwer, 1959. 122 pages, 20 figures, 9 tables, index, paperbound. Price: Not listed.

This doctorate thesis, emanating from Prof. Hagedoorn's clinic, is the most complete and practical ophthalmologic monograph on low vision aids now extant. Credit for help is given Dr. Gerald Fonda, head of the Low-Vision Clinic at the New York Lighthouse. In this investigation of 200 patients, optical aids were considered for only those patients who succeeded in reading eight-point print accurately and six-point print with only occasional errors. Of those examined, 149 (75 percent) were enabled to reach this standard and of these 128 accepted and used the optical aid. Of 35 patients with acuity of 10/200 to 4/200, 23 were given reading ability. With an acuity of only 4/200, an illuminated spectacle magnifier of $\times 10$ to $\times 12$ magnification is necessary. If this proves ineffective, no further magnification is of value.

Of the 200 patients, 75 percent were over 40 years of age. Of these the largest group had senile macular degeneration and only half could be adequately helped. However, all 17 cases of juvenile macular degeneration responded well, though 30 percent refused the indicated aid. The stand magnifier, available with aspherical lenses in $\times 2$, $\times 3$, $\times 5$, and $\times 7.5$ magnification (Igard), proved to be the most acceptable instrument, especially with older persons (81 cases). A typist can place the stand magnifier on the reading matter, leaving both hands free for typing. The semispherical glass loupe (Dutch Visolett, $1.8 \times M.$) is of advantage to those with 20/200 or more acuity, particularly if reading is best in diffuse light as with nuclear cataract and cloudy cornea. Illuminated stand magnifiers are available in high magnifications $\times 8$, $\times 10$, $\times 12$ (Keeler). Hand magnifiers up to +20D. have a special field of usefulness. With one the patient can read maps at 20 inches, conveniently check the

work in the typewriter or read a book in an easy chair.

While a strong monocular plus lens can be prescribed for young intelligent persons, older patients rarely succeed in maintaining a steady focus. The practical limit of a high plus correction is +32D. (plastic aspherical). In weaker powers the clerical form recommended by Fonda is preferable as it allows the reader to look about the room. Only one pair of telescopic spectacles was prescribed as an aid to near vision. For stationary use for distant vision, the De Wohler telescopic spectacles give the highest magnification, $\times 3.5$, and can compensate a spherical refractive error of +5.0D. to -5.0D. by adjustment of the objective.

E. van Maanen-Helmer, Ph.D., is responsible for the excellent English translation but being no ophthalmologist he has give optical terms a strange rendering, using for example "diffracted lens" for bent lens, "prism degrees" for prism diopters. The International Congress of Ophthalmology has yet to make ophthalmic prescriptions universally uniform. An example of the Dutch method for instance is: R sph -7.5 cyl -2 axis 0°. The text is reasonably complete, but projection apparatus and triple aplanat inserts are not described. An American edition, suitably edited and amplified, would fill a real need.

James E. Lebensohn.

CLINICAL EVALUATION OF NEW DRUGS.

Edited by S. O. Waife, M.D., and Alvin P. Shapiro, M.D. (written by 15 authors). New York, Hoeber-Harper, 1959. 216 pages, index. Price: \$7.50.

The universally favorable reviews in general medical literature of this important work have inspired me to seek it out and bring it before my fellow ophthalmologists for their intention and instruction. There is no disappointment. It is a work that should be read and studied by every ophthalmolo-

gist. In these days of a spate of new new drugs and wide claims of their manufacturers, some good and some not so good, we are compelled for the protection of our patients and our own selves, to have authoritative information. This is it.

Dr. Waife is head of the Medical Editorial Department, Lilly Research Laboratories, and Dr. Shapiro is assistant professor of Clinical Science and Medicine, University of Pittsburgh School of Medicine, Pittsburgh. Their work here as editors is outstanding and a prime example to other editors on how such a work should be done. The other authors are widely known and authoritative:

W. B. Beau is physician-in-chief, University Hospitals, State University of Iowa; H. K. Beecher is professor of research in anesthesia, Harvard University Medical School; K. H. Beyer, Jr., is vice president in charge of life sciences, Merck, Sharp and Dohme. He is also a teacher in Temple University and the University of Pennsylvania Graduate School of Medicine.

H. F. Dowling is head of the Department of Medicine, College of Medicine, University of Illinois. J. L. Gabrilove is associate professor of medicine, State University of New York Downstate Medical Center, Brooklyn. D. S. Ingle, Ph.D., is professor of physiology, University of Chicago; Nathan S. Kline is assistant professor of clinical psychiatry, Columbia University College of Physicians and Surgeons, New York.

Louis Lasagna is head of the Division of Clinical Pharmacology, The Johns Hopkins University School of Medicine. Thomas E. Machella is associate professor of medicine, University of Pennsylvania School of Medicine. Paul Meier, Ph.D., is associate professor of statistics, widely known for his excellent work in this field, at the University of Chicago. E. L. Severinghaus is professor of public health and nutrition, Columbia University, and Steward Wolf is professor and head of the Department of Medicine, University of Oklahoma School of Medicine.

This is truly a constellation of stars who scintillate under the capable editing of Waife and Shapiro.

The first part of the book deals with the principles of drug evaluation and the second with clinical trials in practice. An apt quotation of A. Bradford Hill introduces Part I:

In general it will be seen that the essence of a successfully controlled clinical trial lies in its minutia—in a painstaking, and sometimes very dull, attention to every detail.

The introduction to Part II is a quotation from Galen:

All who drink of this remedy recover in a short time, except those whom it does not help, who will die. Therefore, it is obvious that it fails only in incurable cases.

It is a scary and yet optimistic book. It rightly encourages conservatism, at the same time experimentation, but only under the most rigid and scientific control. One is a much better physician for having read and studied it. Obviously quacks should avoid it for they will lose their brazen self-confidence.

Derrick Vail.

SYNOPSIS OF OPHTHALMOLOGY. By William H. Havener, M.D. St. Louis, C. V. Mosby Company, 1959. 282 pages and index. Price: \$6.75.

The latest offering on the principles of ophthalmology for the nonophthalmologic reader is a handsomely bound, well-printed volume of almost pocket size. Its ostensible purpose is to aid general physicians in the understanding and treatment of some of the important diseases of the eye. Copiously illustrated with excellent photographs and drawings and simply and concisely written it would appear to fulfill that aim. It is doubtful that it is adequate for use as a textbook for undergraduate medical students since it does not include any detailed anatomy nor any real information on errors of refraction. Material is not arranged in typical textbook style and perhaps the originality of presenta-

tion makes for a more refreshing approach. The first chapter, on eye examination, is followed by others on diagnosis and treatment of eye injury, diagnosis and management of the red eye, medical ophthalmology, neuro-ophthalmology, glaucoma, strabismus, uveitis, degenerative conditions of the eye, developmental anomalies of the eye, the meaning of eye symptoms, eyelids, physiology, therapy, value of consultation and referral, surgery of the eye, and a final chapter entitled "blindness is preventable."

There are a number of statements to which exception might be taken such as the indictment of the staphylococcus as the commonest cause of "pink eye," the recommendation of 500 mg. of Diamox intravenously at *hourly intervals* in acute glaucoma, and the overemphasis of diabetes as a common cause of xanthelasma. In general, however, the text is accurate and noncontroversial. The book should prove of value to general physicians to whom an ophthalmologist is not readily available.

William A. Mann.

VITAMIN A. By Thomas Moore, Sc.D. (Cantab.) and D.Sc. (Belfast). Amsterdam, Elsevier Publishing Company, 1957. Available from D. Van Nostrand Company, Inc., Fourth Avenue, New York 10. Price: Not listed.

No one should treat eyes without knowing more about the amazing vitamin A, its precursor the carotenes, and the multitude of ways it affects the human body, from conception to old age.

The effects of deficiencies of vitamin A—deficiencies due to poor intake, poor absorption, poor assimilation—are attested by hundreds of papers given by careful scientists and reviewed interestingly and with skill.

Those who attest a new disease entity with corneal destruction, like familial dysautonomia, should read this work; and not only

those but all who are interested in what the body needs and can do to help and preserve the eyes in effective performance.

It does not go into the observations, soon to be published, given at the Brussels Congress of Ophthalmology where I showed that there is a chronic and an acute fulminating deficiency, the latter often associated with some vitamin-A depleting acute general disease, such as smallpox or a diarrhea. In the former is the well-known metaplasia from columnar mucous secreting epithelium to squamous epithelium with keratinization and the latter with acute necrosis of the interstitial corneal substance leading to lysis of the entire cornea and even sometimes attacking the sclera.

This book should be in every ophthalmic, E.N.T., and pediatric library.

Victor Rambo.

EDUCATION AND HEALTH OF THE PARTIALLY SEEING CHILD. By Winifred Hathaway. (Revised by Franklin M. Foote, M.D., Dorothy Bryan, and Helen Gibbons.) New York, Columbia University Press, 1959, edition 4. 201 pages, 27 plates, 14 figures, bibliography, index. Price: \$5.00.

Mrs. Hathaway, who was awarded the Leslie Dana Medal for her outstanding achievements in behalf of the partially seeing child, died on December 1, 1954, just before the publication of the third edition of her classic work. The trio responsible for the present revision are dedicated authorities who have fulfilled expertly the task of providing the latest authentic information in this field.

The first classes devoted to the education of partially seeing children were established in Europe at the instigation of the ophthal-

mologists, Bishop Harman of London (1908) and Edmond Redslob of Strasbourg (1911). The first classes in America were established in 1913—in Boston first and then in Cleveland. By 1940, such classes had extended to the principal cities of the world. Modern educators would like to substitute the term, "special educational facilities for the partially seeing" for the now intrenched but equivocal designation of "sight-saving classes."

Among the 7,310 children in classes for the partially seeing, the chief causes for the impaired vision were developmental anomalies, such as congenital cataract, dislocated lens, albinism, congenital glaucoma, and retinitis pigmentosa.

For all concerned with the welfare of the partially seeing child, which certainly includes ophthalmologists, teachers, and parents, this book is invaluable.

James E. Lebensohn.

THE ETIOLOGY AND CONTROL OF PROGRESSIVE MYOPIA. By Hunter Heiner Turner, M.D. Privately printed, 1959. 113 pages.

While this small volume contains several other papers, mostly of ancient vintage, the principal offering concerns the author's theories as to the etiology of progressive myopia. Based upon the theories of Fischer he has attempted to prove that the essential factor in its production is a biochemical change producing a chronic edema of the sclera with mechanical venous obstruction and passive congestion of the choroidal and retinal vessels and weakening of the sclera. In spite of a valiant attempt to prove this hypothesis he has not produced adequate evidence to substantiate his theory.

William A. Mann.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

1

ANATOMY, EMBRYOLOGY, AND COMPARATIVE OPHTHALMOLOGY

Conrads, H. **The innervation of the normal and the paralyzed ocular muscle.** Arch. f. Ophth. 161:214-218, 1959.

The innervation of the extraocular muscles was studied in histologic preparations. Conrads describes reticulate non-myelinated vegetative fibers and myelinated motor fibers and sensory elements. Pathologic changes were demonstrable in a segment muscle which had been extirpated in abducens paresis. (3 figures, 8 references) F. H. Haessler.

2

GENERAL PATHOLOGY, BACTERIOLOGY, IMMUNOLOGY

Braude, A. I. **Mechanism of action of a toxic bacterial antigen.** Tr. Am. Acad. Ophth. 63:634-641, Sept.-Oct., 1959.

Gram negative bacteria manifest their toxic effects through a lipopolysaccharide component. This endotoxin causes fever, diarrhea and shock. It injures the reticuloendothelial system by both an immediate and a delayed reaction. It produces a leukophoresis followed by stimu-

lation of replenishment at a rate four times faster than normal. Fever is probably produced by liberation of endogenous pyrogen from neutrophils.

A tissue hypersensitivity was found in children without demonstrable circulating antibodies. This very much resembled the reaction to tuberculin, the passive transfer behavior, and the pathologic picture at skin test sites. (4 figures, 18 references)

Harry Horwich.

Lepow, I. H. **Natural resistance to infection: the properdin system.** Tr. Am. Acad. Ophth. 63:628-633, Sept.-Oct., 1959.

The development of the properdin concept is explained. This reaction is an additional mechanism for defense against infection and requires 1. properdin, a serum protein which is one of the heavy gamma globulins, 2. magnesium ions, and 3. all four components of complement.

Gram negative bacteria are in general most susceptible to this system. Certain viruses, such as the mumps virus or influenza viruses A and B, are susceptible whereas the polioviruses and adenoviruses are not. (31 references)

Harry Horwich.

Schwab, F. **The antibody content of the cornea after local medication with antibiotic. III communication. The agglutinin or precipitin content of the cornea after subconjunctival injection of chloramphenicol.** Arch. f. Ophth. 161:298-308, 1959.

After both corneas of rabbits had been immunized by the application of typhoid vaccine or beef albumen, one eye was subsequently given several injections of chloramphenicol (20 mg. given five times) and the other eye injections of normal sodium chloride solution.

Corneal extracts of eyes which had been treated with chloramphenicol showed no significant difference in agglutinin or precipitin content from those of similarly immunized but untreated eyes in a control group. This was also true of eyes which had been treated with penicillin or streptomycin (see communications I and II).

Similarly the agglutinin or precipitin content of the serum of animals which had been treated with chloramphenicol was no different from that of the control group. These findings agree with those of authors who have been unable to find a change in immunity reactions after medication with antibiotics. (3 tables, 14 references)

F. H. Haessler.

Thygeson, Phillips. **Ocular viral diseases.** Med. Cl. North America 43:1419-1440, Sept., 1959.

Thygeson summarizes our knowledge of ocular viral disease and describes the lesions that occur. (11 figures, 37 references)

F. H. Haessler.

3

VEGETATIVE PHYSIOLOGY, BIOCHEMISTRY, PHARMACOLOGY, TOXICOLOGY

Armaly, M. F. **Effect of parasympathetic stimulation on the anterior segment of the cat's eye.** Tr. Am. Acad. Ophth. 63:752-760. Nov.-Dec., 1959.

In this study the ciliary muscle was

found to consist of four groups of fibers, an external meridional, an intermediate trabecular, a circular group medial and forward, and finally some fibers in the ciliary processes just lateral to the ciliary epithelium. A fenestrated series of lattice-like sheets made up the trabeculae, and the number and position of these sheets was demonstrated to affect the aqueous outflow.

Stimulation of the ciliary ganglion produced constriction of the pupil, bulging forward of the center of the lens, retroplacement of the root of the iris with deepening of the chamber angle independent of pupil size, separation and fanning of the trabecular fibers, and reduction of the resistance to outflow. The reverse is produced by section of the preganglionic trunk to the ciliary ganglion. Contraction of the ciliary muscle pulls the trabecular meshwork backwards and medially. These fibers are truly the tendon of the ciliary body. (6 figures, 2 references)

Harry Horwich.

Carapancea, M., Simionescu-Carapancea, S. and Nicolesco, C. **Comparative study of retinal vasomotor reactions by experimental pharmacodynamic investigations and by clinical researches on puerperal eclampsia.** Arch. d'ophth. 19:496-506, July-Aug., 1959.

The authors cite the lack of definitive studies on the effect of medications on the retinal vessels and report continuation studies on both animal and human subjects. They conclude that strychnine, eserine, atropine, pilocarpine, benzedrine, and adrenalin studied comparatively by ocular and cortical application act centrally on the retinal vessels only. They further conclude that in puerperal eclampsia vasomotor changes in the retinal vessels are due to excitation of vasomotor centers prior to the excitation of nuclei controlling skeletal muscle activity, a finding which is in accordance with the com-

mon finding of transient retinal angiospasm early in the disease. The authors found that chloral hydrate diminished the activity of central centers in both animal studies and clinical studies of eclampsia. (2 references)
P. Thygeson.

Gramberg-Danielsen, B. **The reafference principle in its significance for ophthalmology.** Arch. f. Ophth. 161:192-213, 1959.

In an introductory segment of this article the author discusses the reafference theory which differs from the reflex theory in that it expands the concept of the reflex arc by adding to the afferent and efferent arcs a third factor, namely reafference, which provides cortical cooperation for integration. In a second segment he shows how problems in ophthalmology are clarified by this factor of reafference. (3 tables, 46 references)

F. H. Haessler.

Kleinfeld, O. and Hockwin, O. **The dependence of the in vitro absorption of oxygen of lenses on the oxygen content of the nutrient solution.** Arch. f. Ophth. 161:248-251, 1959.

With the increasing partial pressure of oxygen in the nutrient solution an increasing amount of oxygen is absorbed by the lenses of old and young cattle and of rabbits. With the former the oxygen consumption in relationship to the increasing partial pressure of the oxygen in the nutrient solution is expressed in a curve with two steps which suggest the presence of two mechanisms of reaction which depend upon oxygen. (2 figures, 4 tables, 2 references)
F. H. Haessler.

Laffers, Z. and Bozsóky, S. **Significance of the determination of C-reactive protein in inflammatory eye diseases.** Szemészet 96:101-108, 1959.

There is no relationship between CRP level of the serum and the location or the clinical activity of inflammatory eye dis-

eases. During the fever therapy of uveitis, a shortlasting, marked rise of CRP values occurs. CRP was found in the aqueous humor in 11 of 32 patients with uveitis. The appearance of CRP in the anterior chamber is unrelated to the etiology or morphology of ocular inflammation. On the basis of quantitative determinations of total proteins, a relative increase of CRP in the chamber was observed in some cases which might be ascribed to intraocular CRP production.

Gyula Lugossy.

Lugossy, Gy. **The role of the nervous system in fluorescein permeability.** Szemészet 96:108-120, 1959.

The changes occurring in the function of the blood-aqueous barrier, that is, in the vegetative center of the eye (Amsler) suggest the mediatory and regulatory role of the nervous system. The observation that fluorescein permeability readily changes when acted upon by external or internal stimuli raised, many years ago, the idea that neural influences could explain these phenomena. Although the functional examinations and the experiments of Wessely, Linksz and others spoke in favour of such influences several decades ago, their morphologic basis has but recently been demonstrated by Kurus. The investigations of Pavlov and his pupils threw light on the pertinent problems of allergy and the effect of antigens on permeability.
Gyula Lugossy.

Pienkow, M. A. **Influence of nicotinic acid on the blood vessels of the uvea and the retina.** Klinika Oczna 29:11-13, 1959.

Three patients with atrophy of the retinal pigment were examined for changes of the blood pressure level in the retinal and choroidal vessels after administration of nicotinic acid. Ophthalmodynamometry was used. After intravenous injections of 1 cc. of 2 percent solution of nicotinic acid an increase of pressure of 5 to 10 mm. Hg appeared lasting 3 to 5 minutes. It was

followed by a decrease of pressure of 10 to 15 mm. Hg which gradually returned to normal. (1 figure, 4 references)

Sylvan Brandon.

Schenk, H. **Experimental and clinical studies of the possibility of the resorption of gaseous substances from the vitreous.** Arch. f. Ophth. 161:252-281, 1959.

Injection of air into the vitreous for the treatment of retinal detachment has been used since Gonin's time and has been widely used in the diathermy operation. In the author's studies the time of resorption of air and the effect of air injection on ocular tension were measured. The time of resorption of various gases was determined and histologic studies were carried out.

The resorption of air from the vitreous after postoperative injection was complete in seven to 13 days. The injection of air into the vitreous is accompanied by a considerable rise in ocular tension which returns to its previous state in four to six hours. Of various other gases used nitrogen required the longest for resorption but is actually so little different from air that it has no practical advantage. To determine the route of exit from the vitreous the air to be injected was marked with radium emanation. The route was determined by means of autoradiographs. Histologic examination of bulbi enucleated after air injection revealed no changes in the tissue of the vitreous other than a non-specific cell reaction of the connective tissue as an expression of a moderate bland inflammation. The measurement of the hydrogen ion concentration in the vitreous after the injection of various gases revealed no significant changes in pH from which one may conclude that the injection of air or other gases does not bring about swelling of the substance of the vitreous. (15 figures, 4 tables, 93 references)

F. H. Haessler.

Stepanik, J., Auerswald, W., and Dole-schel, W. **The permeation of the aqueous**

by proteins and lipoproteins. Arch. f. Ophth. 161:282-289, 1959.

Each batch of aqueous from 500 to 1,000 bovine eyes was concentrated by dialysis with gum acacia or by ultrafiltration. The proteins were studied by means of electrophoresis and of sedimentation and flotation analysis. The quantitative distribution of albumen and globulin differed negligibly from that in plasma but that of the "heavy component" and lipoprotein lead to a deduction as to the permeation of the barrier between the chamber and the bloodvessel. (5 figures, 2 tables, 26 references)

F. H. Haessler.

Trichtel, F. and Trichtel, H. **Basic investigation for iodine therapy of the eye. II. Microchemical study of the ocular tissues after local and general therapy.** Arch. f. Ophth. 161:290-297, 1959.

The distribution of iodine in the tissues was determined by chemical analysis in 96 eyes of rabbits after application of iodine orally, by intravenous or muscular injection, inhalation, iontophoresis, spraying of cornea, eye cup, subconjunctival or retrobulbar injection, ointment or eye drops. The authors tabulate the availability-quotient which states the portion of substance which appears in the aqueous after its enteral or parenteral exhibition. The data show that more iodine enters the eye from fluids applied to the eye than after oral or parenteral therapy. Local therapy is therefore preferred. (3 tables, 9 references)

F. H. Haessler.

Vassilev, I., Dabov., S. and Rankov, B. **A study of the action of ergotone on the eyes. Acquired and congenital cataracts produced experimentally by ergotamine.** Arch. d'ophth. 19: 524-528, July-Aug., 1959.

Cataract due to ergot poisoning was first described in 1862 by Meier in an epidemic involving 23 of 283 individuals who had consumed the mushroom *Claviceps purpurea*. The cataract is described as

initially nuclear, with eventual opacification of the cortex. The authors studied the effect of ergotamine on the Chinchilla rabbit and describe both congenital and acquired cataract due to this drug. The lens opacity involved the nucleus and posterior cortical layers. The study is illustrated by six plates in black and white. (6 figures, 3 references) P. Thygeson.

Wulf, Ehrich. **Sensibility of the muscle and fixation.** Arch. f. Ophth. 161:185-191, 1959.

The author measured the movements of deviation of the fixating eye in the dark in the primary position, in 30° abduction and in 30° adduction. He used the method of Marx (1913) with exploitation of after-images. The movements of deviation are significantly greater in retrobulbar anesthesia. The results indicate an influence of muscle sensibility on the movements of deviation of the eye during dark adaptation. (3 tables, 22 references)

F. H. Haessler.

4

PHYSIOLOGIC OPTICS, REFRACTION, COLOR VISION

Calmettes, Deodati, Delfour and Bechac. **Amblyopia without strabismus.** Ann. d'ocul. 192:849-862, Nov., 1959.

There are many cases of amblyopia without apparent strabismus or pathologic changes in the retina and the authors divide these into three groups. In Group I is "cryptic strabismus" where the angle of deviation is very small and corresponds exactly to the angle of eccentric fixation. This may be found by special testing with a haploscope and by a method of after-images. In Group II are marked anisometropia and consequent aniseikonia. Group III contains the remaining cases in which no etiology can be found. Illustrative cases are cited for each group. (22 references)

David Shoch.

Halpern, L. **Simultaneous visual and tactile illusions of size.** Confinia neurol. 19:301-305, 1959.

The visual illusions associated with homonymous hemianopsia are provoked by left-sided Jacksonian fits. The tactile illusions are probably an accompanying phenomenon which is secondary to the dominant visual experience. (9 references)

F. H. Haessler.

Krzyzagorska, Halina. **Treatment of complications of high myopia with extract of aloe.** Klinika Oczna 29:75-78, 1959.

The author used an aqueous extract of the leaves of aloes (Biostgmin) in 40 patients with high myopia which was complicated by vitreous opacities in 12, macular exudates in 11, degenerative changes of the choroid and the retina in all 40 and lowered color recognition in 22. Treatment consisted of 30 to 40 injections of 1 cc. every second day. In no case did the eyes become worse; in 12 patients it remained the same and in 28 there was definite improvement of function with some recession of exudates and decrease of vitreous opacities. Improvement in the visual fields, particularly for colors, was noted. The author concludes that severe affection with organic changes cannot be helped but in earlier cases stimulation by retinal enzymes improves its function. Myopia is not affected by the treatment. The treatment is only symptomatic and may have to be repeated. It is also without any danger. (11 references)

Sylvan Brandon.

Pelz, Itta. **The dependence of visual acuity in the parafovea and the contiguous periphery on the wave length and intensity.** Arch. f. Ophth. 161:219-236, 1959.

The point visual acuity was measured 2 to 10° retinotemporally for red, yellow, green and blue filtered light with 82-second points and out to 6° with 41-second points. The increase in the minimum sepa-

rabile in the transition from 2 to 16° peripheral took place in the most accurate observer in the separable zone which coincided with the retinal zones recognized by Polyak. Among other data that emerged is the fact that the just recognizable minimal shifting of the test point was 5° or one half of the diameter of a cone. (3 figures, 3 tables, 20 references)

F. H. Haessler.

Plattner, F. **The frequency of congenital defects of the red-green sense in Persian Aserbeidschan.** Arch. f. Ophth. 161:237-238, 1959.

The author tested 994 pupils with the anomaloscope; 4.5 percent showed defects of the red-green sense. The relative frequency of deuteranomaly in relation to protanomaly was below the European average. (2 tables, 2 references)

F. H. Haessler.

5

DIAGNOSIS AND THERAPY

Aird, R. B. **The retinal circulation as an index of cerebral circulation from the viewpoint of the neurologist.** Angiology 10:193-198, Aug., 1959.

The author points out the importance of a study of the retinal circulation since it reflects a corresponding disease process in the cerebral hemisphere in a high percentage of patients. However, there are other conditions in which the correlation is only fair or even poor. Examination with the ophthalmodynamometer has great value.

F. H. Haessler.

Anderson, K. **Asepsis in ophthalmology.** Tr. Ophth. Soc. Australia 18:74-77, 1958.

A medical bacteriologist describes the characteristics of *Pseudomonas pyocyanea* and the manner in which it thrives inside taps, in the interstices of corks and in many reputed antiseptic solutions. The paper includes a discussion of the bacteriologic aspects of a number of routine

surgical practices such as contaminated scrubbing brushes, germicidal soaps and detergents, face masks, and autoclaves.

Ronald Lowe.

Crompton, D. O. **Asepsis in ophthalmology.** Tr. Ophth. Soc. Australia 18:63-73, 1958.

The incidence of postoperative ocular infection in Adelaide is reviewed. During 1949 to 1958 of 1,077 lens extractions performed by 20 ophthalmologists eight eyes were lost from endophthalmitis. Possible causes, such as nasal carriers, cross infection, and infected eye drops are discussed. Prevention of sepsis is described and stressed. Cultures from 61 bottles of eye drops showed 11 grossly contaminated with *Pseudomonas pyocyanea* and one with *Staphylococcus aureus*.

Ronald Lowe.

Emeryk, B. and Warecka, K. **Ocular symptoms in multiple sclerosis.** Klinika Oczna 29:43-46, 1959.

The authors examined 242 patients with multiple sclerosis and found 137 with ocular symptoms either in form of the retrobulbar neuritis or muscle paralysis. The authors suggest that when an ophthalmologist treats a patient with these symptoms and also some additional neurologic symptoms, even as mild as paresthesia or slight disturbance of gait, the patient should be directed to a neurologist for a complete examination because of possible multiple sclerosis. Four cases are described in detail for illustration. (1 table, 15 references)

Sylvan Brandon.

Gans, Bruno. **The pupillary membrane in premature infants.** Arch. Dis. Childhood 34:292-297, Aug., 1959.

The presence and extent of a pupillary membrane is a valuable index of immaturity in premature infants. (8 figures, 5 references)

F. H. Haessler.

Hugonnier, M. R. and Hugonnier-Clayette, S. **The reeducation of binocular vision.** *J. de méd. de Lyon* 40:671-674, Sept. 5, 1959.

The authors point out that reeducation, though time consuming, is indispensable in strabismus and amblyopia. They describe the procedure. F. H. Haessler.

Jayle, G. E., Junod, S. and Valette, J. **Ocular and general circulatory troubles before and after treatment with a retarding pancreatic hormone.** *Ann. d'ocul.* 192:801-838, Nov., 1959.

An extract of pig pancreas is described which apparently causes a fall in blood pressure and an intense vasodilation when given intramuscularly or intravenously. Its action is chiefly on the arterioles and capillaries. A group of 63 patients was treated with this material, 35 of whom had vascular disease of the eyes. Changes in the vascular state were determined by two methods. One was the observation of histamine blebs on the legs after injection of fluorescein and the second a recording of the visual field under reduced illumination (mesopic fields). Other tests were performed as well. The authors conclude that there is great improvement in the vascular state with this therapy. Subjective visual improvement is quite common with frequent mention of the disappearance of vitreous floaters. Visual fields showed improvement and it is stated that only two patients out of 35 showed no ocular improvement. The material employed is termed "Kalliecrein" by its originators.

David Shoch.

Lamb, A. **Blood changes associated with penetration of the globe with particular reference to monocytosis and sympathetic ophthalmia.** *Tr. Ophth. Soc. Australia* 18:114-120, 1958.

An analysis is made of monocyte counts in several diseases and in patients with different intraocular operations or trau-

matic eye perforations. The monocyte counts were quite unaffected by the clinical state of the human eye. The use of white blood cell counts to assist prognosis of injured eyes needs careful review.

Ronald Lowe.

Leopold, M. **Ophthalmologic signs in atherosclerosis.** *J. de méd. de Lyon* 40:683-692, Sept. 5, 1959.

The author reviews the ocular complications of atherosclerosis which are chiefly ischemia or infarction of retina, choroid, or the optic tracts. He suggests that there is also a relation between atherosclerosis and cataract, glaucoma, and lesions of the iris.

F. H. Haessler.

Leopold, P. **Localization of intraocular foreign bodies by transpupillary diaphanoscopy.** *Ann. d'ocul.* 192:863-867, Nov., 1959.

The author reverses the usual procedure of transillumination to localize intraocular foreign bodies. He places the cone of a powerful transilluminator on the cornea and the shadow of minute foreign bodies can be seen on the sclera and marked. This method is effective even in the presence of cloudy media and cataracts. (2 figures, 4 references)

David Shoch.

Papadopoulos, A. **New method of fixation of regard by the patient during skiascopy and ophthalmoscopy.** *Ann. d'ocul.* 192:868-873, Nov., 1959.

The author places a reflecting red and green disc (Scotchlite) on either side of his visual acuity chart. These discs are modeled after reflecting road markers. They are placed about 120 cm. apart and about 170 cm. from the floor. He feels that they provide excellent fixation targets for skiascopy and ophthalmoscopy.

David Shoch.

Ryan, H. **Asepsis in ophthalmology.** *Tr. Ophth. Soc. Australia* 18:77-80, 1958.

A general account is given of the possible sources of postoperative infection.

Ronald Lowe.

Vancea, P. and Tudor, E. **Late intraocular infection following an Elliot trephine.** Arch. d'opht. 19:529-532, July-Aug., 1959.

The authors report an intraocular infection occurring during the course of a subacute conjunctivitis in an eye operated upon three and one-half years previously for glaucoma. The infection involved the trephine bleb and there was immediate loss of vision but intensive treatment with penicillin, cortisone, atropine, and injection of milk led to healing and return of vision. The specific cause of the infection was not determined. The literature on late infection is reviewed and the authors recommend as a prophylactic measure the immediate treatment of any conjunctivitis that develops in an eye which has been operated upon. They also recommend that surgery be performed in such a way as to provide as thick a covering over the trephine bleb as possible. The flap should include episcleral tissue. (4 references)

P. Thygeson.

6

OCULAR MOTILITY

Breinin, G. M. **Contributions of electromyography to strabismus.** Proc. Inst. Med. Chicago 22:303-310, July 15, 1959.

The author's analysis of data is a contribution to an understanding of disturbances of muscles rather than a diagnostic aid.

F. H. Haessler.

King, F. P. **Paralyses of the extraocular muscles in diabetes.** Arch. Int. Med. 104:318-322, Aug., 1959.

Three cases of paralysis of the ocular muscles seen in private practice within five years are reported. In the first diabetes was not suspected and the possibility of intracranial neoplasm or aneurysm was

considered until the condition rapidly cleared. In the second case the consultant rapidly recognized the presence of previously unrecognized diabetes. In the third patient the diabetes had been poorly controlled for several years. (19 references)

F. H. Haessler.

Pfandl, E. **Refraction changes after surgery on the extraocular muscles.** Wiener med. Wchnschr. 109:648-649, Aug. 22, 1959.

In 102 eyes of 63 patients changes in refraction were noted after surgical procedures on the extraocular muscles but the changes occur only after procedures which shorten or strengthen the effect of a muscle. These changes in refraction may be a cause of defective vision.

F. H. Haessler.

Molnár, K. **Modern therapy of strabismus from the point of view of the practitioner.** Szemészet 96:141-144, 1959.

Treatment should be initiated as early as possible. In case of congenital strabismus, spectacles and occlusion are well tolerated from the age of one and one-half or two years onward. If binocular vision is to be secured, the fixating eye (in cases of alternation alternately) should, after a subtotal correction in cycloplegia, be occluded until the strabismus has ceased. Occlusion is to be done for the following reasons: 1. if it is faithfully maintained for two to three months, vision becomes greatly improved or nearly completely restored even in cases of severe amblyopia, and 2. in cases of alternating strabismus alternating occlusion should be continued in order to combat the faulty binocular sensory associations. When patients come later orthoptic treatment is introduced at the age of three to four years, because 1. sufficient time is then available for the stabilization of the angle of strabismus while the correcting glasses are used, and operation can still be performed, 2. the

mental development of the child permits orthoptic therapy, and 3. the latter therapy can be achieved before school age. When the angle of strabismus has become stable, operation, if it cannot be avoided, should not be postponed. It is mainly in cases of severe strabismus that the treatment which consists of several operations should be begun early, so as to accomplish it before the age of five and one half years because the child must have sufficient time and opportunity to build up and stabilize the intricate binocular reflex with parallel eyes. After the age of six years, the possibility of this gradually decreases.

Gyula Lugossy.

7

CONJUNCTIVA, CORNEA, SCLERA

Bucher, U. G. and Reid, L. **Sjögren's syndrome—report of a fatal case with pulmonary and renal lesions.** *Brit. J. Dis. Chest* 53:237-252, July, 1959.

The authors describe a fatal case of keratoconjunctivitis sicca which was complicated by pulmonary and renal lesions. (9 figures, 48 references)

F. H. Haessler.

Crompton, D. O. **The treatment of symblepharon by means of split skin grafting.** *Tr. Ophth. Soc. Australia* 18:110-113, 1958.

Three cases are described. (5 figures)

Ronald Lowe.

Pavlou, A. T. and Wolff, H. G. **The bulbar conjunctival vessels in occlusion of the internal carotid artery.** *Arch. Int. Med.* 104:53-60, July, 1959.

The bulbar conjunctival vessels in patients with occlusion of the common or internal carotid artery were studied. On the side of the lesion the bulbar conjunctiva showed dilated arteries and arterioles and venules, relative paucity of minute vessels and decreased velocity of the blood flow. The unilateral alterations in the

bulbar conjunctival vessels were not seen in patients with thrombosis of other intracranial arterial branches or of the central artery of the retina. (8 figures, 15 references)

F. H. Haessler.

Rutkowski, Slawomir. **The problems of corneal transplants.** *Klinika Oczna* 29:15-26, 1959.

Experiments conducted on 26 rabbits showed that the primary aqueous has no tendency to clot. Immediately after the emptying of the anterior chamber primary aqueous starts reforming but after 2 to 2½ minutes streams of dense fluid appear which after 20 to 60 seconds contain suspended red cells. Secondary aqueous starts clotting where this dense fluid is. The author found that this fluid is made of the lymph which pours out of tissues of the iris and the ciliary body because of considerably disturbed hydrostatic conditions resulting from their damage. The time and location of the clotting depends on the areas where the lymph comes out and also explains where synechia tend to form after surgery on the rabbit eye.

Sylvan Brandon.

8

UVEA, SYMPATHETIC DISEASE, AQUEOUS

Blodi, F. C. **Sympathetic uveitis as an allergic phenomenon.** *Tr. Am. Acad. Ophth.* 63:642-649, Sept.-Oct., 1959.

Blodi studied 62 cases of sympathetic uveitis at the University of Iowa and compared them with 91 cases from the Armed Forces Institute of Pathology and 17 cases from Wills Eye Hospital. About one quarter of these, or more, were associated with phacoanaphylactic reactions. This was taken to be evidence for an allergic component in sympathetic uveitis. The history of uveal pigment sensitivity was also briefly reviewed in elucidating this picture.

A pathologic study of three sympathiz-

ing eyes was made. One, interestingly, followed evisceration of the fellow eye. In all cases the typical picture of sympathetic uveitis was seen. (6 figures, 29 references)
Harry Horwich.

Drozdowska, Stanisława. **A rare case of an iris cyst in an infant.** *Klinika Oczna* 29:83-86, 1959.

The author presents a case of congenital cyst of the iris in a six-month-old child. The cyst was found in the lower nasal quadrant of the left iris. Paracentesis of the cyst was without result because of an increase in the intraocular pressure. The author excised the cyst together with the contiguous part of the iris. Recovery was uneventful. (2 figures, 2 references)

Sylvan Brandon.

Musial, Albin. **An operation for congenital pupillary membrane.** *Klinika Oczna* 29:91-93, 1959.

Persistent pupillary membrane in both eyes of a child who was three years of age is described. The membrane had a spider-like appearance with the body of the spider located in the center of the pupil but unattached to the lens. The membrane was removed surgically by entering the anterior chamber with a keratome, picking up the strands with a muscle hook and cutting them with the iris scissors. After surgery the pupils were round, clear and they reacted well to light.

Sylvan Brandon.

Serpell, G. **New vessel formation in the iris.** *Tr. Ophth. Soc. Australia* 18:97-104, 1958.

A series of 47 cases of iridic neovascularisation is recorded. Two thirds were due to either central retinal vein thrombosis or diabetes mellitus. Glaucoma was present in a high percentage of affected eyes and fellow eyes. Gonioscopic appearances and morphological evolution of rubeosis iridis are considered.

Ronald Lowe.

Weekers, R., Bonnet-de Rudder, M. and Bassleer, J. **Clinical forms of toxoplasmic chorioretinitis.** *Arch. d'opht.* 19:481-495, July-Aug., 1959.

The authors consider in detail the serologic and clinical criteria for the diagnosis of toxoplasmic chorioretinitis. They report a serologic study of 256 normal Belgian individuals varying in age from six months to 80 years. By means of the Sabin dye test (technique of Lelong and Desmonts) they found a positive serology varying from 1.53 percent in the 0 to 9 age group to 66 percent in the 60+ age group. On this basis they consider the test as highly significant in the young but of decreasing significance in the older patients. They analyze the case histories of 20 cases of suspected toxoplasmic chorioretinitis found in a two-year period at the University of Liège and conclude that it is justifiable to divide toxoplasmosis cases into three groups, as follows: 1. the congenital cicatricial chorioretinitis of the young child, 2. the congenital recurrent chorioretinitis of the adolescent, and 3. the acquired chorioretinitis of the adult. The lesions of the different types are illustrated by 12 fundus drawings in black and white. The authors speculate on the mode of contagion in the adult form and discuss daraprim, combined with sulfadiazine, as a therapeutic agent, without reaching a conclusion as to its efficacy. (6 figures, 1 table, 1 graph, 24 references)

P. Thygeson.

Zeydler, Lucyna. **A case of atypical congenital iris coloboma.** *Klinika Oczna* 29:87-90, 1959.

The author presents a case of congenital malformation of the iris in both eyes of a man, 33 years of age. The coloboma in the right eye was in the lower temporal quadrant and that in the left eye was in the upper nasal quadrant. The sphincter and dilator muscles were also underdeveloped and there was no change in the size of

pupils even after application of myotics or mydriatics. The presence of congenital lenticular opacities and the remnants of the pupillary membrane gave further evidence of congenital malformation of the anterior segments of the eyes. (1 figure, 4 references)
Sylvan Brandon.

9

GLAUCOMA AND OCULAR TENSION

Hycnar, Maria. **Types of elastometric curves in glaucoma.** *Klinika Oczna* 29:27-35, 1959.

The author examined 96 eyes of 50 patients with glaucoma to obtain elastotonomograms. Four types of curves were found and most of the time characteristics of more than one type were seen in each patient. Normal curves were found only in patients with compensated glaucoma. The characteristics of the four types follow:

Type I: Longer than normal curve, more than 12 mm., most frequently seen in acute attacks of glaucoma.

Type II: Shorter than normal curve, less than 8 mm., in cases where treatment resulted in compensation.

Type III: Broken line with disproportionate parts.

Type IV: Starting point above 20 mm. Hg.

Types III and IV usually mean abnormal reaction of the reflex mechanism. The author concludes that elastometric testing has high diagnostic value and after repeated testing permits correct diagnosis in 97 percent of cases of glaucoma. (4 figures, 2 tables, 7 references)

Sylvan Brandon.

Lowe, R. **Acute glaucoma requiring lens extraction.** *Tr. Ophth. Soc. Australia* 18:120-123, 1958.

Acute glaucoma may be caused by the following lens conditions: dislocation, phacolysis, intumescence, malignant glaucoma. Lens extraction is required to cure the attacks.
Ronald Lowe.

Serpell, G. **Tonometer standardisation.** *Tr. Ophth. Soc. Australia* 18:136-137, 1958.

The principles of tonometer standardisation are outlined and the services available in Melbourne, Australia are noted.
Ronald Lowe.

Valu, L. **Comparative evaluation of cyclodialysis and cyclanaemization.** *Szemészet* 96:125-132, 1959.

Blaskovics' cyclodialysis inversa was, with Kettesy's modification, applied to 102 patients, and the results were compared with those of Kettesy's cyclanaemization performed on 137 patients. Advantages of cyclodialysis are 1. it can be applied to nearly all kinds of glaucoma and 2. it can be repeated several times on the same eye. Its drawbacks are 1. numerous complications which are frequently fatal such as bleeding, cataract, cyclitis, and vitreous prolapse, 2. decrease of vision and postoperative myopia, and 3. contraction of visual fields. Advantages of cyclanaemization are 1. no intra- or postoperative complication occurs, 2. there is no postoperative decrease of vision or visual field, 3. if glaucoma simplex is attended by good vision (above 0.6) and low initial tension (below 40 mm. Hg), the operation is successful in almost 100 percent, and 4. if no improvement ensues, the operation can be repeated after four or five days without any danger. Its drawbacks are 1. its field of indication is less than that of cyclodialysis and 2. overdosage may be followed by undue cicatrization and a wedge-shaped atrophic spot on the iris.
Gyula Lugossy.

10

CRYSTALLINE LENS

Altamirano, R. and Calahan, A. **Alpha-chymotrypsin in cataract surgery: an operative and postoperative study in 80 cataract extractions.** *South. M. J.* 52: 1327-1330, Nov., 1959.

The authors have used alpha-chymotrypsin in 123 cataract extractions and report their experiences in 80 (consecutive) cataract extractions that were followed for at least three months. Preoperative complications were noted in 31 of the 80 eyes, and were chiefly glaucoma, uveitis, diabetes and endothelial dystrophy. The most frequent of the operative complications were rupture of the hyaloid with or without vitreous loss and rupture of the lens capsule. Striate keratitis and moderate uveitis were the most common postoperative complications.

A "control" series of 31 patients is included in which cataract extraction was performed without alpha-chymotrypsin in one eye and with it in the other eye; the results in these two groups are compared. The authors found that the use of alpha-chymotrypsin makes delivery of the lens easier, and offers better prognosis for avoiding rupture of the lens capsule and loss of vitreous, but is not without certain definite hazards. Their surgical technique is described in detail and also illustrated. (1 figure, 2 tables, 6 references)

Joseph H. Derivaux.

Elliot, A. J. **A cataract operation in a centenarian.** *Canad. M. A. J.* **81**:247-248, Aug. 15, 1959.

This experience is reported because it is so rare. The patient had useful vision restored and lived another 15 months.

F. H. Haessler.

Kozłowski, Bogumil. **Treatment of simultaneous glaucoma and cataract.** *Klinika Oczna* **29**:69-74, 1959.

The author observed seven cases of glaucoma with cataract, five cases of glaucoma in aphakia, five after discission and 10 cases of cataract in glaucoma. Glaucoma due to cataract was cured by removal of the lenses. Cyclodialysis was beneficial in aphakia though sometimes the operation had to be repeated; this

operation was also successful in eyes in which discissions were performed. In the cases of cataract in glaucoma, extraction of the lens with iridectomy and cyclodialysis or trephining usually controlled the tension and restored the function of the eye. Visual results depended essentially on the stage of glaucoma in which the treatment was started.

Sylvan Brandon.

Lugossy, Gy. **Cataract operations with alpha-chymotrypsin and the erysiphake.** *Orvosi Hetilap* **100**:831-832, 1959.

Thirty-seven successful cataract operations have shown that Barraquer's alpha-chymotrypsin (Quimotrase) possesses an elective zonulolytic effect without damaging the capsule or the borderline membrane of the vitreous body. After incising the cornea with a Graefe knife, 2 ml. of a fresh solution of alpha-chymotrypsin 1:5000 is injected behind the iris. Two minutes later the lens becomes globe-shaped and protrudes toward the chamber. This is the sign of complete enzymatic zonulolysis. Then the lens lying freely on the limiting membrane of the vitreous is removed with an erysiphake without difficulty. By this method intracapsular extraction of the lens can be achieved regardless of the age of the patient and the stage of the cataract.

Gyula Lugossy.

Németh, L. **The aging eye.** *Szemészet* **96**:120-124, 1959.

The symptoms pointing to the aging of the eye are summarized in an anatomic order. From a practical point of view, great attention is called to the fact that the small subcapsular vacuoles arising in the axial part of the lens are characteristic of old age, although their significance is rarely recognized, mainly because they cannot be seen but by means of a slit-lamp. Slight complaints of old people, such as deficient skill in fine work, slight

blurring of the margins of objects seen, halo, coloured halo surrounding lights, and the sight of more than one moon are often due to these vacuoles. The assumption of latent glaucoma or early degeneration of the macula is not necessary if a small subcapsular vacuole is revealed.

Gyula Lugossy.

Sampaolesi, R. **Two new signs that indicate the syndrome of "exfoliation of the lens capsule"** *Ann. d'ocul.* **192**:839-848. Nov., 1959.

The authors feel that "exfoliation of the lens capsule" is a misnomer and that actually there is a deposit of material (cells, pigment, debris) on the lens, iris, and trabeculum. They offer two signs that support this and enable one to make an early diagnosis of exfoliation. One sign is an increased permeability of the blood-aqueous barrier as demonstrated by the fluorescein test. The second is a dispersion of iris pigment with deposition of this pigment in the angle, specifically, the pigment deposits on the posterior surface of the cornea anterior to Schwalbe's line in the form of waves. This occurs before deposits can be seen on the lens and iris. (8 figures, 11 references) David Shoch.

11

RETINA AND VITREOUS

Alström, C. H., Hallgren, B., Nilsson, L. B. and Aasander, H. **Retinal degeneration combined with obesity, diabetes mellitus and neurogenous deafness; a specific syndrome (not hitherto described) distinct from the Laurence-Moon-Bardet-Biedl syndrome; a clinical, endocrinological and genetic examination based on a large pedigree.** *Acta psychiat. et neurol. Scandinav.* **34**:supp. 129, 1959.

The authors provide a monographic discussion. (4 figures, 49 references)

F. H. Haessler.

Fischer, Franz. **Diabetic retinitis proliferans. Report of 100 cases.** *Arch. f. Ophth.* **161**:239-247, 1959.

The author analyzes his findings in 100 cases of diabetic retinitis proliferans. He compares his findings with those of other investigators and evaluates them. He discusses several questions which concern the essential nature of the disease and he suggests a new concept as to the heredo-familial nature of the disease. (27 references)

F. H. Haessler.

Greer, C. H. **Pathology of pseudoglioma.** *Tr. Ophth. Soc. Australia* **18**:36-43, 1958.

The following conditions are discussed—Coats' disease, angiomatosis retinae, endophthalmitis, developmental defects, and miscellaneous conditions. The paper is followed by discussion by C. Swan.

Ronald Lowe.

Hallgren, Bertil. **Retinitis pigmentosa combined with congenital deafness; with vestibulo-cerebellar ataxia and mental abnormality in a proportion of cases—a clinical and genetico-statistical study.** *Acta psychiat. et neurol. Scandinav.* **34**:supp. 138, 1959.

The author provides a thorough clinical and statistical study. (3 figures, 48 references)

F. H. Haessler.

Hobbs, H. E., Sorsby, A. and Freedman, A. **Retinopathy following chloroquine therapy.** *Lancet* **2**:478-480, Oct. 3, 1959.

The authors describe a retinopathy which they ascribe to chloroquine therapy.

F. H. Haessler.

McGavie, J. S. **Retinoblastoma.** *Pediat. Cl. North America* **6**:359-367, May, 1959.

The author provides a short description of diagnosis, prognosis and treatment. (4 figures)

F. H. Haessler.

Mettier, S. R., Jr. **Retinal manifestations of systemic diseases.** Postgrad. Med. 26:162-166, Aug., 1959.

Mettier points out that ophthalmoscopy is a useful procedure for the practitioner and describes the more important findings.

F. H. Haessler.

Meyer-Schwickerath, G. **Indications and limitations of light coagulation of the retina.** Tr. Am. Acad. Ophth. 63:725-738, Nov.-Dec., 1959.

The records of 1,000 patients treated by light coagulation are reviewed. In general terms the high development of the Zeiss instrument is described. Macular holes are historically of greatest interest. In only 20 percent of such cases is there deterioration of the visual acuity and this is only slight. Peripheral retinal holes are closed easily if the retina can be brought close to the choroid either by bed rest or by surgical means. In cases of less than two months duration, 10 to 20 percent of retinal detachments can be brought into apposition by bed rest with binocular bandages. In cases of peripheral degeneration a new ora can be made by one to 200 coagulations. This restricts the field by 5 to 10 degrees so the upper nasal barrage should be as peripheral as possible.

In perforating injuries with clear media, light coagulation is superior to surface diathermy. This should be done ten days prior to removal of a foreign body.

Retinal blood vessels are easily coagulated. Vessels in the vitreous are more difficult, but can be closed to prevent recurrent vitreous hemorrhage.

A wide variety of tumors has been treated. Malignant melanomas do not respond to radiation but can be obliterated by this method. Breast tumors also have been treated. Good results have been obtained in retinoblastomas and in angiomas of the retina. Aneurysms and hemangiomas respond as do iris tumors and skin

and conjunctival neoplasms. It is of interest that xanthelasma can be extirpated without scar formation, since the overlying skin is not affected by this process.

Of 490 patients without detachment who were treated prophylactically only 14 developed detachments. Treatment was unsuccessful in only 37 of 333 cases of detachment. In 111 cases of Eales' disease, 89 eyes remained free from severe hemorrhage. Of 121 patients with fundal neoplasms almost all were treated successfully; 63 artificial pupils were fashioned and 26 patients had improved visual acuity without subsequent surgical procedure. (7 figures, 1 table)

Harry Horwich.

Paufique, L. and Spira, C. **Preventive treatment of retinal detachment.** J. de méd. de Lyon 40:657-662, Sept. 5, 1959.

Though 70 percent of eyes with retinal detachment recover after surgical treatment, there still are many patients in whom vision is not restored. Detachment in both eyes occurs almost exclusively in patients who have severe myopia or who have had surgery for cataract. In such eyes preventive treatment is indicated and several techniques the results of which have been satisfactory are described.

F. H. Haessler.

Phillips, F. **The rising incidence of diabetic retinopathy.** Tr. Ophth. Soc. Australia 18:92-96, 1958.

The increasing incidence of blindness due to diabetic retinopathy is said to be caused by depot insulins and hypoglycaemia—not by longevity. The author is strongly attacked in the discussion following his paper.

Ronald Lowe.

Royer, M. J. **Retinal manifestations of virus infection.** J. de méd de Lyon 40: 675-682, Sept. 5, 1959.

In the course of a virus disease the

retina is frequently affected. Periphlebitis occurs in the course of Behçet's disease, obstruction of the central retinal artery in herpes zoster, septic neuritis in the pneumopathies, and chorioretinal lesions in Harada's disease and in pigmentary pseudoretinitis. F. H. Haessler.

Van Eck, W. F. **Effect of a low fat diet on the serum lipids in diabetes and its significance in diabetic retinopathy.** *Am. J. Med.* 27:196-211, Aug., 1959.

The effect of a diet containing only 20 grams of fat per day was noted in 12 diabetics with retinopathy and elevated serum lipids. It seems justifiable to use strict low-fat diet in such patients.

F. H. Haessler.

Wagener, H. P. **Measurement of retinal arterial pressure (progress of medical science).** *Am. J. M. Sc.* 238:211-230, Aug., 1959.

This excellent extensive summary is an integration of recent work. (154 references)

F. H. Haessler.

12

OPTIC NERVE AND CHIASM

Swietliczko, Irena. **Picture of the optic disc in low intraocular pressure.** *Klinika Oczna* 29:37-42, 1959.

The optic disc becomes edematous after the decrease of the intraocular pressure which occurs after surgery or a perforating injury. A similar appearance is sometimes encountered in seemingly normal eyes. The author investigated the intraocular pressure of the eyes, the ocular blood pressure, and the behavior of secretion and outflow of the aqueous. The author examined 229 students and in 10 of them low intraocular pressure was found. In all of them there was some degree of edema of the disc made evident by slight elevation of the disc, blurred margins, vascular tortuosity and congestion. Five cases of pseudoedema were seen in

the patients of the clinic. In all of them there was low intraocular pressure of 6 to 12 mm. Hg, low diastolic arterial pressure and increased outflow of intraocular fluid. (15 references) Sylvan Brandon.

13

NEURO-OPHTHALMOLOGY

Bishop, P. O., Burke, W., Davis, R., and Hayhow, W. R. **Binocular interaction in the lateral geniculate nucleus. A general review.** *Tr. Ophth. Soc. Australia* 18: 15-35, 1958.

Histologic and anatomic evidence confirms the concept that in the lateral geniculate nucleus information from each eye is kept carefully segregated. Afferent fibers from each optic nerve end in different cell laminae. Even for one eye different kinds of information are probably kept separate in the different laminae associated with that eye. In the cat, however, at least some direct binocular integration probably occurs in the lateral geniculate nucleus. Histologic studies show that direct binocular interaction is limited to the zones in the nucleus that contain large cells. These regions which contain large cells may be concerned with cortically mediated reflexes associated with binocular fixation whereas the remainder of the nucleus is concerned with the first stages of "conscious" visual perception.

By recording from single cells and axons, three different binocular processes of interaction in the lateral geniculate nucleus have been distinguished 1. direct interaction—a small number of cells receiving afferents directly from both eyes that can be fired by the separate stimulation of both optic nerves; 2. delayed interaction—these few cells can be fired by the separate stimulation of either optic nerve but only with latencies which indicate that the afferent impulses must have traversed one or more synapses because there are two groups of cells, and very

complex afferent paths may be involved, and 3. indirect interaction—probably impulses from one eye can nearly always alter the firing pattern of a cell discharged by impulses from the other eye. These neuronal circuits are almost certainly extrageniculate and very complex.

Although the lateral geniculate nucleus is organized for segregation of the information as it arrives directly from each eye, considerable binocular integration also occurs in the nucleus in the later stages of central visual integration. The circuits involved in the latter process are almost certainly extrageniculate and probably traverse the cerebral cortex. There are widespread direct and indirect connections between the cortex and the lateral geniculate nucleus which can be demonstrated both histologically and electro-physiologically.

The view that the lateral geniculate body is no more than a relay station on the pathway between eye and cerebral cortex must be abandoned. At present, the phylogenetic evidence suggests that direct binocular interaction in the lateral geniculate nucleus progressively diminishes in the higher animals. Ronald Lowe.

Kjellin, Kage. **Familial spastic paraplegia with amyotrophy, oligophrenia, and central retinal degeneration.** Arch. Neurol. & Psychiat. 1:133-140, Aug., 1959.

The author describes an apparently new clinical entity as it occurred in two pairs of brothers. It is characterized by non-progressive mental retardation, spastic paraplegia which became manifest at 25 years of age and made rather slow progress, a slowly progressing amyotrophy due to a peripheral neurogenic lesion, and a characteristic retinal degeneration. There were small atrophic foci with displacement of pigment in and about the macula. The onset of the retinal changes was late and progressed slowly.

F. H. Haessler.

Oates, J. K. and Hancock, J. A. H. **Neurological symptoms and lesions occurring in the course of Reiter's disease.** Am. J. M. Sc. 238:79-84, July, 1959.

The authors describe one case of "shoulder girdle" neuritis, one of meningo-encephalitis, and one with symptoms of nerve root pain, each occurring in association with an attack of Reiter's syndrome. Reiter's syndrome is characterized by a venereally transmitted nonspecific urogenic infection and recurrent relapsing polyarthritis. (9 references)

F. H. Haessler.

Skrzypczak, Kazimierz Edmond. **A case of virus encephalitis and meningitis as complication of the ocular herpes zoster.** Klinika Oczna 29:79-82, 1959.

The author presents a case of encephalitis and meningitis following ophthalmic herpes zoster in a man, 75 years of age. Symptoms started on the left side of the face affecting the skin and the cornea. Symptoms of general infection were also present. On the ninth day paresis of the third and fourth cranial nerves appeared and were followed by exophthalmus and swelling of the lids. After a few days of improvement the general condition of the patient became worse and the symptoms of meningoencephalitis became evident. At the beginning the patient was given penicillin which was changed to aureomycin. Gradual improvement led to almost complete recovery after almost two months of hospitalization. When he left the hospital the patient still had weakness of the lower branches of the left facial nerve and the muscles of the left eye. (15 references) Sylvan Brandon.

Woodworth, J. A., Beckett, R. S., and Netsky, M. G. **Hereditary ataxia: a familial disorder with features of olivopontocerebellar atrophy, Leber's optic atrophy, and Friedreich's ataxia.** Arch. Int. Med. 104:594-606, Oct., 1959.

This disorder was noted in four of six male members of a family.

F. H. Haessler.

14

EYEBALL, ORBIT, SINUSES

Halmy, K. **Paragonimiasis retrobulbaris.** Szemészet 96:133-136, 1959.

After a short review of paragonimiasis from a clinical aspect two cases are reported in which a retrobulbar cyst was removed. In both, the bulbs were preserved and good vision was attained. General examination for paragonimiasis was done in the second case only. In this patient the likelihood of a primary pulmonary location was demonstrated as well as the orbital one, and the examination of the sputum was positive.

Gyula Lugossy.

15

EYELIDS, LACRIMAL APPARATUS

Abbie, A. A. **Hinc illae lacrimae.** Tr. Ophth. Soc. Australia 18:43-51, 1958.

An anatomist discusses evolution, comparative anatomy, development and abnormalities of the lacrimal system.

Ronald Lowe.

Böles, S. **Therapy of congenital atresia of tear pathways.** Szemészet 96:137-140, 1959.

Congenital atresia of the lacrymal ducts and concomitant dacryocystitis can be cured without risk and within a short time in the majority of cases. If the conservative procedures fail, external dacryocystorhinostomy can be performed in hibernation also in early childhood.

Gyula Lugossy.

Fralick, F. B., Berke, R. N., Crawford, J. S., and Schimek, R. A. **Symposium: Ptosis Complications.** Tr. Am. Acad. Ophth. 63:657-682. Sept.-Oct., 1959.

Fralick, F. B. **Surgical anatomy physiology, and the three main operative approaches.** pp. 657-662.

The anatomy of the upper lid is described and points are brought out for emphasis. The orbital septum is separated from the levator aponeurosis by a wedge of orbital fat above the tarsus. If the septum is resected with the levator, severe lagophthalmos on downward gaze will result. Whitnall's levator check ligament is lucidly described. Müller's muscle is said to be the chief support of the tarsus. If dissection from Müller's is not carried posteriorly onto the surface of the globe, the fornix will not prolapse. No more than 5 mm. should be resected from the tarsus lest bowing or entropion occur. (3 figures, 8 references)

Harry Horwich.

Iliff, C. E., Berke, R. N., Crawford, J. S., Schimek, R. A. **Discussion:** pp. 663-682.

Berke stated that the optimum age for surgery is from three and a half to five years. The operation of choice is levator resection. When this is inadvisable and the ptosis is bilateral, frontalis suspension should be used; if it is unilateral superior rectus suspension is advised. In treating jaw winking by any method a large part of the levator should be resected. The amount of levator action present is measured by holding the brow and having the patient look up and down with a millimeter rule held before the eye. When levator action is poor more effect is obtained by using the skin route for resection and when it is good one should use the conjunctival approach. This is because one can reach back further through the skin approach, the levator can be advanced on the tarsus, and the sutures are less likely to stretch. The skin approach is also easier. Overcorrection is treated by making an incision 20 to 25 mm. long

through the tarsus and one millimeter from its upper edge. This is deepened until the wound gapes two to three times the amount of overcorrection. An intermarginal suture is then placed to maintain it at this level.

Various complications in levator resection described were loss of lashes from a skin incision too far down; necrosis of the lid margin from the clamp; overaction of the inferior oblique from damage to the superior oblique tendon; trapping of the reflected oblique tendon; overcorrection (this disappears if the operation is done through the conjunctiva for congenital ptosis but not after skin incisions or acquired ptosis); redundant skin which can be excised; and trapping of Whitnall's check ligament. The check ligament should be freed, except in cases of congenital ptosis with good levator action, in order to avoid lagophthalmos nasally. Prolapse of the conjunctival fornix is avoided by placing a gut suture through the upper fornix and the tendon of the superior rectus at the start of surgery. Exposure keratitis is avoided by covering the cornea with the lower lid by means of cellophane tape brought from the cheek to the brow, rather than Frost sutures. In ptosis due to a lacerated levator the muscle is more easily found via the skin route. The tissue should be biopsied to be sure it is muscle.

Schimek presented his results in 115 patients treated by means of the Iliff technique. In senile ptosis (ptosis myopathica) one should resect very little in order to avoid overcorrection. Excellent results were obtained in 66 percent of congenital ptosis, 20 percent of acquired hereditary ptosis and 50 percent of acquired traumatic ptosis. Like Berke he treats jaw winking by excision of the levator and use of the superior rectus. Surgery for an incomplete third-nerve paralysis should not be done until at least

one year after its onset. One must beware of diplopia or exposure keratitis. Myasthenia and Horner's syndrome do not require surgery. The Iliff procedure is very easy and gives good results even with poor levator action. It is less prone to undercorrection than other techniques. One should correct blepharophimosis before working on the levator or undercorrection will result. Overcorrection can be minimized by removing the rubber pegs used immediately after the operation. In severe cases levator recession is done. Proper lid folds are obtained by passing the levator sutures so that they emerge 3 mm. above the lash line and the subsequent levator retraction produces the fold.

Lagophthalmos is usually present prior to surgery. To avoid postoperative lagophthalmos, methyl cellulose or other protective medications are used. Superior rectus surgery may cause keratitis, muscle imbalance, or lid notching. In patients with very poor levator function that structure can be detached and united to the frontalis.

Crawford uses a two-stage procedure for jaw winking. After excising some of the levator muscle he waits at least two weeks before doing a fascial sling repair. He prefers fascia to a suture as the latter nearly always is followed by infection. Before surgery one should ascertain the position of the lid folds, the status of corneal sensitivity, and Bell's phenomenon. The amount of ptosis can be measured by many methods, in the most ingenious of which the patient is asked to read from a card as it is moved vertically up a perimeter. If the condition is bilateral both sides should be treated at once. One should leave at least 3 mm. of tarsus; removing too much can cause ectropion, although postoperative edema and placement of lid sutures too close to the lid margin may also cause it. The

dressings and sutures are removed the day after surgery. His technique for the use of a fascial sling is described in detail.

Fralick reviewed the indications for levator resection. One cannot give a reliable formula for how much levator should be resected for each millimeter of ptosis. The various major forms of frontalis procedure are briefly reviewed. (2 figures, 1 table)
Harry Horwich.

Mackenzie, J. R. and Patience, C. R. **Papillary cystadenoma of the lachrymal caruncle.** *J. Path. & Bact.* 78:288-289, July, 1959.

One example of this lesion is described which is considered to have arisen from minute lachrymal glands in the area and to be analogous to adenolymphoma of the parotid gland.
F. H. Haessler.

Miratynska-Rusinowa, Elibieta. **Etiology and symptoms of familial ptosis.** *Klinika Oczna* 29:49-56, 1959.

The author discusses two general theories of inheritance of physical characteristics and notes that the dualistic theory of Mendel and Morgan is widely accepted in the literature. Pathogenesis and classification of ptosis are presented in detail. A family consisting of 12 individuals in three generations and having five individuals with ptosis is presented. (2 figures)
Sylvan Brandon.

Ravault, M. and Bonamour, G. **Ocular manifestations in Rendu-Osler's disease.** *J. de méd de Lyon* 40:693-698, Sept. 5, 1959.

The authors briefly summarize the characteristics of this syndrome and then describe more extensively its ocular manifestations. The palpebral and conjunctival telangiectases are typical facial angiomas. Retinal lesions are much less frequent and often of a questionable nature. The authors classify the lesion as clinical

angiomatosis which involves elastic tissue.
F. H. Haessler.

Rogers, P. A. **Surgery of the lids.** *Tr. Ophth. Soc. Australia* 18:105-109, 1958.

Neoplasms of the eyelids should be treated surgically by ophthalmologists. Three case histories are presented.

Ronald Lowe.

Ryan, E. **Naso-lachrymal surgery and polythene tubes.** *Tr. Ophth. Soc. Australia* 18:51-53, 1958.

Seventeen operations with the use of Summerskill's plastic tube are reported and the three failures are described in detail.
Ronald Lowe.

Spaeth, E. B. **Tumors of the lacrimal gland.** *Tr. Am. Acad. Ophth.* 63:739-751. Nov.-Dec., 1959.

This is a cogent appeal for early and radical surgical treatment of lacrimal gland tumors. At least 90 percent of the tumors are considered to be mixed-cell. It is pointed out in diagnosis, that inflammatory signs may be present in cases of tumor and absent in cases of simple inflammation. It is noted that bilateral neoplasms, aside from lymphoma, have never been reported. Great stress is placed on the necessity of careful and planned microscopic study as being the only means for definitive diagnosis. Benign and malignant conditions can mimic each other with distressing verisimilitude.

The examination should be augmented by careful, skilled roentgenologic study of the bony orbits. The surgical exposure should be bold and adequate; the best approach is that of Krönlein. The gland should be removed intact in its capsule, and any accessory or adjoining glands or lobules should be sought for and removed equally carefully. Despite this radical approach, the mortality rate in mixed-cell tumors remains about 50 percent.

In the discussion Henderson noted that the incidence of malignant mixed tumor was not so high in his series. He also advised that a small dose of radiation could be used to rule out lymphomas.

Zimmerman found 50 percent of tumors to be benign mixed, 15 percent malignant mixed, and 35 percent other carcinomas. In the benign group there were no deaths, in the malignant there were two and in the carcinomas, 15. (3 figures, 3 tables, 12 references)

Harry Horwich.

down, a saucer-like widening was provided at the upper end. Complications were numerous and help of an otolaryngologist was necessary. The tube could form a false route and not open into the nasal cavity. Most frequent was a slight dropping of the tube and blocking of its end by the swollen nasal mucous membrane. Three tubes were extruded but the ducts remained patent. Six case histories are presented for illustration. (1 figure, 7 references)

Sylvan Brandon.

Strzyzewski, Kazimierz. **A case of blocked tear ducts treated by implantation of bird's feather.** *Klinika Oczna* 29: 95-99, 1959.

The author describes a case of blocked tear ducts in which the usual dacryocystorhinostomy could not be done because of a small tear sac. A prosthesis made of a bird's feather was used to connect the tear sac with the nasal cavity. The result was satisfactory for four months after which the patient did not return for inspection. (3 figures, 7 references)

Sylvan Brandon.

Tye, A. A. **Tumours of the lachrymal sac.** *Tr. Ophth. Soc. Australia* 18:132-136, 1958.

A review is presented and a case report in which a diagnosis of papilloma of the lachrymal sac was made. Ronald Lowe.

Wilk-Wilczynska, Maria and Borsuk, Josept. **Results of intubation of tear ducts of patients of the Medical Academy in Lodz.** *Klinika Oczna*: 29:1-9, 1959.

Blocked tear ducts were treated by intubation during the years 1956 to 1958; 65 operations were performed which were successful in 77 percent after first time, and 80 percent after additional operations. First the tubes were long (over 20 mm.) and made of vinyl; later shorter nylon tubes were used. To prevent dropping

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TUMORS

Holman, C. B. **Roentgenologic manifestations of glioma of the optic nerve and chiasm.** *Am. J. Roent.* 82:462-471, Sept., 1959.

The roentgenograms were studied in 48 patients with glioma of the optic nerve or chiasm or both. It was found that an estimate of the size and extent of the suprasellar tumor may be obtained by pneumoencephalography and ventriculography.

F. H. Haessler.

17

INJURIES

Mondelski, Stanislaw. **Treatment of penetrating eye injuries with typhoid vaccine.** *Klinika Oczna* 29:57-67, 1959.

The author evaluates the results of treatment with typhoid vaccine of 398 penetrating eye injuries. Injuries are divided into three groups. In the first group of clean fairly superficial wounds with little or no infection superficial healing is usually without complications. Typhoid vaccine in such cases is only an additional useful factor in the recovery from the injury. In the second group are large wounds with prolapsed tissues, with the introduction of infectious material into the eye, and with an intraocular foreign body deep in the posterior segment of the eye. Injuries

in the very young who do not cooperate and in whom the start of treatment is delayed also belong to the same group; even energetic treatment is without result and prognosis is poor from the beginning. Typhoid vaccine is useless in these cases. In the third group are all those cases in which prognosis is uncertain because they exhibit features of both previous groups at the same time. Appropriate treatment is very important and the vaccine may be of great help. After initial improvement endophthalmitis may eventually cause the loss of the eye. (3 figures, 2 tables, 8 references) Sylvan Brandon.

18

SYSTEMIC DISEASE AND PARASITES

Abrahamson, I. A., Jr. and Abrahamson, I. A. **Diabetes mellitus—associated ophthalmic changes.** Ohio St. M. J. 55: 1111-1919, Nov., 1959.

The authors point out that "diabetes is diagnosed earlier by the astute physician during routine ophthalmoscopic examination." (2 references, 20 figures)

F. H. Haessler.

Blief, A. and Siegel, P. **Fundus changes in preeclampsia and eclampsia.** Med. Klin. 54:1462-1464, Aug. 14, 1959.

Regular ophthalmoscopic examinations showed that the degree of fundus change depends less on the severity than on the duration of the eclampsia.

F. H. Haessler.

Bonamour, G. and Gaillot. **The ocular complications of varicella.** J. de méd. de Lyon 40:663-670, Sept. 5, 1959.

Palpebro-conjunctival, corneal and uveal lesions are described. In patients with the encephalitis of varicella the optic and the oculomotor nerves may be affected. Embryopathic lesions may occur in the infant when a pregnant woman has varicella.

F. H. Haessler.

Palmer, R. F., Searles, H. H. and Boldrey, E. B. **Papilloedema and hypoparathyroidism simulating brain tumor.** J. Neurosurg. 16:378-384, July, 1959.

Two cases of this syndrome are described. With treatment for the hypoparathyroidism the increased intracranial pressure, papilledema, and other neurologic manifestations subsided. The mechanism of the production of the increased intracranial pressure and papilledema are poorly understood. It is possible that elevated serum phosphorus and decreased serum calcium may be related to the development of the syndrome. (28 references) F. H. Haessler.

20

HYGIENE, SOCIOLOGY, EDUCATION, AND HISTORY

Hamilton, J. B. **Eyes and scurvy.** Tr. Ophth. Soc. Australia 18:83-90, 1958.

The author describes the historical importance of scurvy in early Pacific exploration and its control by James Cook following the investigations of Lind. Many cases of infantile scurvy still occur. Haemorrhages into the retina or vitreous are reported in patients over 40 years of age who for various reasons have had dietetic deficiencies.

Ronald Lowe.

Kingsley, J. **Television as a visual task.** Tr. Ophth. Soc. Australia 18:54-62, 1958.

The following aspects are discussed in detail: viewing distance, the brightness of surrounds, the factors that make a good picture, the length of viewing time and its frequency. The paper is unsuitable for abstracting but is full of practical advice and lucid explanations. It describes television principles in general and the Australian system in particular.

Ronald Lowe.

Parmelee, A. H., Jr., Fiske, C. E. and Wright, R. H. **Development of ten chil-**

dren with blindness as a result of retrolental fibroplasia. *Am. J. Dis. Child.* 98: 198-220, Aug., 1959.

In this extensive discussion the authors stress how very important it is to avoid judging the child as mentally retarded and to deprive him of any opportunity for intellectual development.

F. H. Haessler.

Stokoe, N. L. **A European ophthalmic tour.** *Tr. Ophth. Soc. Australia* 18:124-132, 1958.

The author describes visits to Utrecht (Weve), Amsterdam (Hagedoorn), Rotterdam (Flieringa), Lyons (Paufigue).

Ronald Lowe.

Trecolle and Malo. **A study of ophthalmology in mass.** *Arch. d'opht.* 19:507-523, July-Aug., 1959.

The hospital center of Bab Khemis at Marrakech was opened in June, 1953. It is a modern hospital complete with out-

patient department and operating suites, and there are 120 beds assigned to ophthalmology. The hospital is surrounded by a vast shaded patio and by extensive gardens. In 1957 more than 100,000 patients were examined, an average of 350 a day. The authors describe in detail the types of surgical and medical cases encountered. Trichiasis and cataract were the most common surgical eye conditions, and keratoconjunctivitis, xerosis, and vernal catarrh the most common medical conditions. A number of rare lesions were seen and are described in detail. The authors state that in 1958 dacryocystorhinostomy was performed on a large scale and that facial plastic surgery and keratoplasty were given special consideration. They deplore the necessity for the abandonment of a mobile surgical group which for several years performed much necessary surgery for cataract and trichiasis in small villages far from the medical center. (1 table) P. Thygeson.

OPHTHALMIC MINIATURE

A new lower lid has been made in a case of Mr. Bowman's.

The patient, a lad, who had lost the lower right lid (except a very small portion near the outer canthus) after scarlatina, followed by chicken-pox. One of the pustules turned black; the sloughing spread, and it ended in the destruction of the lid; the sclerotic to the lower orbital edge was exposed; the conjunctiva is therefore congested. The skin flap (of the usual shape) was taken from the temple, and measured to reach about a quarter of an inch beyond the inner canthus; it was by numerous sutures attached to the skin of the orbital edge (which previously has been loosened). The angle of the flap near the inner canthus was left free to seek its own attachment; it had a very wrinkled loose appearance, and overlapped the inner canthus by a few lines (sic) the free margin reaching as high as the middle of the pupil. A cotton-wool bandage was applied over the flap.

Dr. Bader,

"Report of some operations,"

Royal Lond. Ophth. Hosp. Reports, 2:112, 1859.

NEWS ITEMS

EDITED BY DONALD J. LYLE, M.D.
411 Oak Street, Cincinnati 19, Ohio

News items should reach the editor by the 10th of the month. For adequate publicity, notices of postgraduate courses and meetings should be received three months in advance.

DEATHS

Dr. Frank Barber, Lima, New York, died October 26, 1959, aged 76 years.

Dr. John Woolfolk Burke, Washington, D.C., died October 5, 1959, aged 75 years.

Dr. Aaron Roth, Brooklyn, New York, died September 9, 1959, aged 72 years.

Dr. Elbert Stetson Sherman, Newark, New Jersey, died September 11, 1959, aged 86 years.

Dr. Henry Lee Sloan, Sr., Charlotte, North Carolina, died November 5, 1959, aged 73 years.

Dr. Eutimio Domenico Tenaglia, Saint Louis, Missouri, died October 12, aged 58 years.

ANNOUNCEMENTS

COURSE IN SLITLAMP BIOMICROSCOPY AND OCULAR SURGERY

The Committee on Postgraduate Education of the Montefiore Hospital, Pittsburgh, announces an advanced course in slitlamp biomicroscopy of the living eye combined with additional courses in slitlamp microscopy, gonioscopy, applanation tenotomy, applanation tonometry, surgery of intraocular foreign bodies, and cataract surgery, to be given by the Montefiore Department of Ophthalmology under the direction of Dr. Harvey E. Thorpe and associates. These courses will be given at the Montefiore Hospital, Pittsburgh, Pennsylvania, for four days, March 28th-31st, inclusive, from 8:00 A.M. to 4:00 P.M. Members of the guest faculty are: Dr. Robert J. Masters, Indianapolis, Mr. Samuel Berman, New York City. For further information, write to A. McNabb, secretary of Postgraduate Ophthalmic Courses, 206 Iroquois Building, Pittsburgh 13, Pennsylvania.

EYE AND EAR DAY PROGRAM

The program for the 1960 Eye and Ear day of the Eye and Ear Hospital of Pittsburgh, scheduled for Wednesday, April 6th, will be devoted to "What's new." The Ear Department has assigned the entire day to presentation of a wide variety of medical and surgical advances. For the ophthalmologist, the latest developments in the management of glaucoma, retinal detachment, cataract surgery and ophthalmodynamometry will be presented. At the evening meeting, Mr. J. F. Fellman, Jr., director of information and research, Health Insurance Association of America, New York, will speak on "Medico-economic trends."

WEST VIRGINIA MEETING

Among the guest speakers on the program for the meeting of the West Virginia Academy of Ophthalmology and Otolaryngology at the Greenbrier Hotel, White Sulphur Springs, West Virginia, April 10th-12th, will be: Dr. Harold G. Scheie, Professor of Ophthalmology, University of Pennsylvania School of Medicine, Philadelphia, "The surgical management of glaucoma: Parts I and II," Dr. Charles E. Iliff, Baltimore, "Adult ocular tumors," Dr. Oscar T. Becker, Chicago, "Plastic surgery in otolaryngology," Dr. Helen J. Ossofsky, Washington, D.C., "Pediatric ocular tumors," and Dr. John T. Dickinson, Pittsburgh, "Modern treatment of otosclerosis."

There is a nonmember registration fee of \$10.00 to cover all the social and scientific sessions. For further information contact the secretary, Dr. A. C. Esposito, First Huntington National Bank Building, Huntington, West Virginia.

WASHINGTON HOSPITAL CENTER

Completing the 1959-1960 series of lectures at the Department of Ophthalmology, Washington Hospital Center, 110 Irving Street, N.W., Washington 10, D.C., will be: "Uveal inflammations," April 23rd and 30th and May 7th. Dr. Alan C. Woods, Baltimore, will speak on April 23rd. His subjects will be "Uveitis: General symptoms; diagnostic problems; therapy." On April 30th, Dr. G. Victor Simpson will discuss "Nongranulomatous specific infections: Clinical behavior; therapy," and Dr. C. Worth Sprunt, "Nongranulomatous specific infections: Pathology." On May 7th, these same speakers will discuss "Granulomatous specific infections."

The final series of lectures will be on the "Orbit." On May 14th, Dr. Melvin G. Alper will speak on "Hemorrhage and aneurysm"; Dr. Bernard H. Zeavin on "Inflammations"; and Dr. Harry M. McAllister on "Tumors." Dr. John W. Henderson, Ann Arbor, Michigan, will discuss "Endocrine disturbances" and "Lipoidal and osseous diseases," on May 21st. Dr. M. Noel Stow will discuss "Surgery of the orbit" on May 28th.

NEW YORK UNIVERSITY COURSES

New York University Post-Graduate Medical School, Department of Ophthalmology, New York, offers the following courses:

Ophthalmoscopy, a part-time course, from 9:00

A.M. to 12:00 M., April 25th through 29th, under the direction of Dr. George N. Wise. This is a study of the normal fundus, congenital anomalies and diseases of the vitreous, retina, choroid, and optic nervehead, as well as traumatic fundus changes and manifestations of general diseases in the eye grounds. Illustrated with Kodachrome slides and case presentations. Tuition is \$60.00.

Histopathology, a part-time course, from 1:00 to 4:00 P.M. April 25th through 29th. This consists of lectures, demonstrations, and microscopic study of exemplary pathologic material. It is introduced with a lecture on general principles of ophthalmic pathology and a system for reading ophthalmic pathology slides. Tuition is \$100.00.

BROOKLYN EYE AND EAR HOSPITAL

A concentrated course in corneal surgery of two and one-half days' duration will be given under the direction of Dr. A. Benedict Rizzuti at the Brooklyn Eye and Ear Hospital on Thursday, Friday, and Saturday, May 12th, 13th, and 14th.

Present surgical concepts of keratectomies and keratoplasties will be stressed. Allied subjects such as beta radiation, contact lenses, operating room photography, instrumentation, and so forth, will be discussed by staff members. Surgical procedures in the operating room will be demonstrated according to availability of donor material. Participants will be offered an opportunity to apply surgical principles on animal eyes.

The course is limited to six ophthalmologists, tuition \$100.00.

Address inquiries to Mr. Henry Williams, superintendent, Brooklyn Eye and Ear Hospital, 29 Greene Avenue, Brooklyn 38, New York.

SEMINAR ON GLAUCOMA

A seminar on glaucoma with particular emphasis on gonioscopy and the study of the anterior angle will be given at the Brooklyn Eye and Ear Hospital on May 16th, 17th, and 18th. Ample opportunity for practical instruction in the use of the gonioscope will be given and material from the glaucoma clinic will be utilized.

The course will be given by Dr. Daniel Kravitz, assisted by Drs. Nicholas P. Tantillo and Samuel Zane. Registration is limited to six ophthalmologists only. Application and the fee of \$50.00 may be addressed to: Dr. Daniel Kravitz, Brooklyn Eye and Ear Hospital, 29 Greene Avenue, Brooklyn 38, New York.

PAN-PACIFIC SURGICAL ASSOCIATION

The eighth congress of the Pan-Pacific Surgical Association will be held in Honolulu, Hawaii, September 27th through October 5th.

All members of the profession are eligible to register and are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities because of limited space.

An outstanding scientific program by leading

surgeons promises to be of interest to all doctors. Ten surgical specialty sections are held simultaneously.

Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, director general of the Pan-Pacific Surgical Association, Suite 230, Alexander Young Building, Honolulu 13, Hawaii.

COURSE IN ORTHOPTICS

The basic course in orthoptics for technicians, sponsored by the American Orthoptic Council, will be held in the Department of Ophthalmology, University Medical Center, Ann Arbor, Michigan, from June 20th to August 13th. As usual, there will be didactic lectures and practical demonstrations given by an outstanding faculty. It is preferred that three months of practical training precede the course. For further information as well as application blanks write to John W. Henderson, M.D., Department of Ophthalmology, University Medical Center, Ann Arbor, Michigan.

ASIA-PACIFIC ACADEMY

The first congress of the Asia-Pacific Academy of Ophthalmology will be held October 10th-13th at the University of the Philippines Medical Center, under the auspices of the Philippine Ophthalmological Society. The theme of the congress will be "Blinding diseases of the Asia-Pacific regions"; the official language will be English. There will be scientific sessions, free papers and medical films. For further information address the secretary, Dr. William John Holmes, Alexander Young Building, Honolulu 13, Hawaii.

AMERICAN COLLEGE OF SURGEONS

The 46th annual clinical congress of the American College of Surgeons will be held in San Francisco, October 10th to 14th. For further information write Dr. William E. Adams, secretary, American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

ACS SECTION MEETING

On the ophthalmic surgery program for the section meeting of the American College of Surgeons (convening in Minneapolis and Rochester, Minnesota, April 11th, 12th, 13th, and 14th) to be held in Rochester, Minnesota, April 14th are: "Problem of eyelid retraction in Graves' disease," Dr. John W. Henderson; "Diagnosis of glaucoma," Dr. Hugo Linden Bair; "Keratome incision and postplaced sutures in cataract surgery," Dr. Thomas J. Kirby, Jr.; "Analysis of results of surgical treatment of strabismus," Dr. T. G. Martens.

MISCELLANEOUS

WILLS CLINICAL CONFERENCE

The 12th annual clinical conference of the Wills Eye Hospital, Philadelphia, was held on February 18th, 19th, and 20th. Dr. Patrick J. Kennedy pre-

sided at the Friday morning session during which papers were presented by Dr. E. Howard Bedrosian, "New operation for small angle squint"; Dr. Leonard Apt, "Endophthalmitis in children due to worm larvae"; Dr. Daniel F. Fisher, "Recent fractures of the orbit"; Dr. Gerard M. Shannon, "Symblepharon repair: Mucous membrane graft." A uveitis symposium was also presented at this session. Those taking part were Drs. H. E. Chodos, Joel B. Chodos, Joseph W. Hallett, Michael I. Wolkowicz, and Irving H. Leopold.

At the afternoon session, Dr. Carroll R. Mullen presided. Papers presented were "Application of the Lieb anterior chamber lens: After three years," Dr. Turgut N. Hamdi; "The surgical aspects of defective adduction," Dr. Edmund B. Spaeth; "Indications for the use of light coagulation," Dr. William S. Tassman.

Presiding over the Saturday morning session was Dr. Edmund B. Spaeth. Dr. Charles G. Steinmetz, III, spoke on "Neuroblastoma simulating retrolental hemorrhage." Drs. Patrick J. Kennedy, James S. Jordan and Joseph F. Morrison presented a paper on "The routine use of Alpha Chymar in cataract extraction." "The value of clinical electromyography in certain neuro-ophthalmologic conditions," was presented by Drs. Thomas R. Hedges and Narendra Krishna and Miss Sibyl Beckitt.

Dr. Wilfred E. Fry presided over the Saturday afternoon session during which Dr. William H. Annesley, Jr., spoke on "Scleral trap door and silicone plate procedure in retinal detachment surgery"; Dr. Arthur H. Keeney on "Classification and surgical techniques in iridectomy."

On the evening of February 18th, Dr. Levon K. Garron, clinical professor of ophthalmology, University of California, San Francisco, presented a lecture on "The trabecular meshwork by electron microscopy," before the Section on Ophthalmology, College of Physicians of Philadelphia.

BOSTON SECTIONAL MEETING

A four-day sectional meeting of the American College of Surgeons was held in Boston February 29th through March 3rd. Presiding over the programs on ophthalmic surgery on February 29th and March 1st were Drs. Edwin B. Dunphy, Thomas Cavanaugh, Dr. William P. Beetham and Dr. Garrett L. Sullivan, all of Boston. Papers presented at the opening session were:

"Some uses of plastic materials in ophthalmology," Dr. William Stone, Jr., Boston; "Management of intraocular foreign bodies," Dr. Murray F. McCaslin, Pittsburgh; "Management of intraocular hemorrhage following contusion," Dr. Arthur G. DeVoe, New York; "Newer sterilizing methods in ophthalmic surgery," Dr. Henry F. Allen, Boston; "The treatment of postoperative infection," Dr. Irving H. Leopold, Philadelphia; "Surgical procedures in the syndrome of epicanthus inversus, blepharophimosis and ptosis," Dr. Carl Cordes Johnson, Boston.

At the Monday afternoon session, Dr. Virgil G. Casten, Boston, gave a lecture on "Orbital surgery"; and Dr. Jin H. Kinoshita, Boston, on "Biochemical approaches to the study of cataracts." A symposium on cataract surgery, under the leadership of Dr. Arthur G. DeVoe, was also held: Dr. Howard F. Hill, Waterville, Maine discussed "Clinical factors involved in the use of zonulolysis"; Dr. Trygve Gundersen, Boston, "The extracapsular operation"; Dr. Paul A. Chandler, Boston, "Surgery of congenital cataracts"; Dr. John S. McGavic, Bryn Mawr, Pennsylvania, "Complications."

Dr. Endre A. Balazs, Boston, opened the panel discussion on retinal detachment with a lecture on "The role of the vitreous body in retinal detachment." Taking part in the panel discussion were Dr. Charles L. Schepens, Boston, moderator; Drs. Samuel T. Adams, Montreal, P. Robb McDonald, Philadelphia, L. Harrell Pierce, Baltimore, and Donald M. Shafer, New York, collaborators.

Preceding a panel discussion on keratoplasty of which Dr. Brendan D. Leahey, Lowell, Massachusetts, was moderator, and Drs. Ramon Castroviejo, New York, John H. King, Jr., Washington, D.C., and R. Townley Paton, New York, collaborators, were lectures by Dr. Garrett Sullivan, Boston, "Minor ophthalmic plastic procedures," and Dr. Harold W. Brown, New York, "Surgical correction of vertical deviations."

Concluding the program was a symposium on glaucoma surgery, with Dr. Virgil G. Casten, Boston, as leader. Speakers were Drs. Harold G. Scheie, Philadelphia, "Open-angle glaucoma"; Paul A. Chandler, Boston, "Angle-closure glaucoma"; and Elmer J. Ballintine, Cleveland, "Tonography in the management of simple glaucoma."

SOCIETIES

NSPB PRESIDENT AND DIRECTORS

Enos Curtin, New York City, was elected president of the National Society for the Prevention of Blindness at its recent annual meeting. He succeeds Ira V. Hiscock, Sc.D., recently retired chairman of the Public Health Department at Yale University. Mr. Curtin is president of the Ophthalmological Foundation and is a member of the board of the New York Association for the Blind.

Other new members of the board of directors to serve for three years are: Mrs. Dorothy Bryan, assistant to the director, Division of Special Education—Blind and Partially Seeing, State Department of Public Instruction, Springfield, Illinois; Ralph E. Dwork, M.D., M.P.H., director of health, Ohio Department of Health, Columbus, Ohio; Edward R. Granniss, manager, Loss Prevention and Engineering Department, Royal-Globe Insurance Group, New York; Mrs. Ronald J. Foulis, chairman, Delta Gamma Fraternity Project on Sight Conservation and Aid to the Blind, Washington, D.C., and Frank W. Newell, M.D., Department of Surgery, University of Chicago, Chicago, Illinois.

Re-elected to the board from the New York area

are: John H. Dunnington, M.D., vice-president of the National Society, consultant in ophthalmology, Presbyterian Hospital, and professor emeritus of ophthalmology, Columbia University; Leonard Greenburg, M.D., commissioner of New York City Department of Air Pollution Control; Thomas H. Johnson, M.D., former clinical professor of ophthalmology, Columbia University, and Richard K. Paynter, Jr., executive vice-president, New York Life Insurance Company.

PERSONAL

Dr. P. K. Basu has been appointed the Stapells Director of Ophthalmic Research in the University of Toronto. This has been made possible through the generosity of Mr. H. G. Stapells, Q.C., of Toronto. The object of the Stapells fund is to further ophthalmic research at the University of Toronto. Dr. Basu will direct and co-ordinate the ophthalmic research in the Department of Ophthalmology and carry on active research himself.

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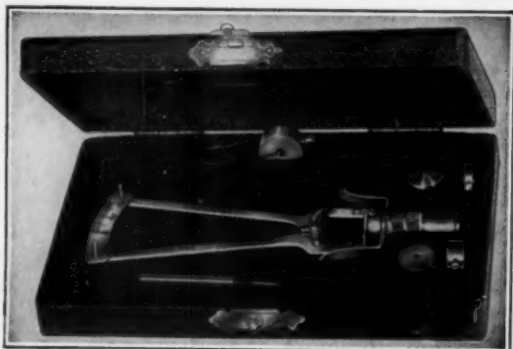
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ABSTRACTS

- Anatomy, embryology, and comparative ophthalmology; General pathology, bacteriology, immunology; Vegetative physiology, biochemistry, pharmacology, toxicology; Physiologic optics, refraction, color vision; Diagnosis and therapy; Ocular motility; Conjunctiva, cornea, sclera; Uvea, sympathetic disease, aqueous; Glaucoma and ocular tension; Crystalline lens; Retina and vitreous; Optic nerve and chiasm; Neuro-ophthalmology; Eyeball, orbit, sinuses; Eyelids, lacrimal apparatus; Tumors; Injuries; Systemic disease and parasites; Hygiene, sociology, education, and history 652

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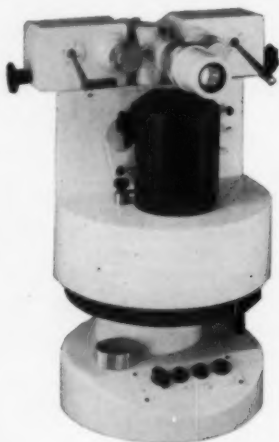
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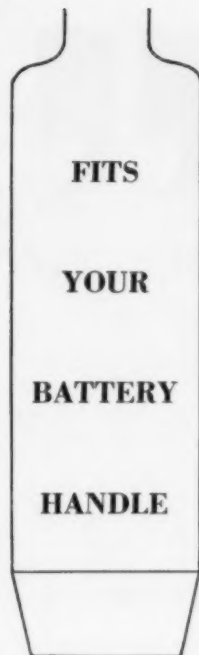
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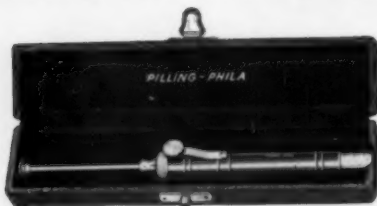
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